A Cation-Directed Two-Component Cascade Approach to Enantioenriched Pyrroloindolines

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1. General information

All NMR spectra were recorded on Bruker AV400, AV500 and DRX500 spectrometers. $^1$H and $^{13}$C NMR spectral data are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). $^{19}$F NMR spectra are referenced relative to CFCl₃. The following abbreviations are used to describe multiplicities s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, sept = septet, br = broad, m = multiplet. NMR spectra were processed in TopSpin 3.1. High resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTOF spectrometer using positive electrospray ionization (ESI), or on a Micromass GCT spectrometer using field ionization (EI/FI) or chemical ionization (CI). IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Absorptions are measured in wavenumbers and only peaks of interest are reported. Melting points of solids were measured on a Griffin apparatus and are uncorrected. IUPAC names were obtained using the ACD/ILab service. Weighing was performed with a 4-decimal place balance. All solvents were dried on a column of alumina prior to use.
2.1 Synthesis of Isocyanides

**General Procedure A:** To a solution of the relevant formamide (1.0 eq) in DCM (1.4 mL/mmole substrate) at 0 °C, triethylamine (2.5 eq) was added. POCl$_3$ (1.0 eq) was then added dropwise, and the reaction mixture was left to stir at 0 °C for 90 min. The reaction was quenched with 10% aqueous sodium carbonate solution and stirred for a further 10 min. The mixture was then diluted with water (5 mL/mmole substrate) and extracted with DCM (3 x 5 mL/mmole substrate). The organic phases were combined, dried over K$_2$CO$_3$ and concentrated *in vacuo*.

**General procedure B:** Methyl isocyanoacetate (1.0 eq) was dissolved in DMSO (6.0 mL/mmole substrate) at room temperature. Cesium carbonate (1.5 eq) was added, and the reaction mixture was stirred for 10 min. The relevant fluoronitrobenzene (1.3 eq) was added, and the mixture was stirred for 16 h at room temperature. The mixture was then diluted with water (10 mL/mmole substrate) and extracted with ethyl acetate (3 x 10 mL/mmole substrate). The organic phases were combined, dried over anhydrous MgSO$_4$ and concentrated *in vacuo*.

**General Procedure C:** Compounds were prepared by modification of a known procedure (Carney, D. W.; Truong, J. V; Sello, J. K. *J. Org. Chem*. 2011, 76, 10279–10285). N,N'-Dicyclohexylcarbodiimide (DCC) (1.3 mmol) was dissolved in DCM at 0 °C and formic acid (1.3 mmol) was added dropwise. Upon addition, a precipitate was formed and the reaction mixture was stirred for additional 10 min. The relevant amino acid methyl ester hydrochloride (1.0 mmol), 4-dimethylaminopyridine (DMAP) (0.2 mmol) and Et$_3$N (1.6 mmol) were added, and the mixture was stirred at room temperature overnight. The reaction was concentrated *in vacuo* and the residue was suspended in EtOAc, filtered through a short silica column and evaporated under reduced pressure. Crude formamide was
dissolved in THF at 0 °C under an argon atmosphere and Et$_3$N (5 mmol) was added. POCl$_3$ (1.5 mmol) was added dropwise over the course of 10 min and the reaction mixture was stirred for 2 hours. The reaction was quenched with 10 % Na$_2$CO$_3$ and was stirred for additional 10 min. The reaction mixture was diluted with EtOAc and washed with brine and water. The organic layer was dried over anhydrous MgSO$_4$ and concentrated *in vacuo*. Pure product was obtained by flash chromatography.

*(Isocyanomethylene)dibenzene*

To a suspension of diphenylmethanamine hydrochloride (2.20 g, 10.0 mmol) in ethyl formate (30 mL), triethylamine (2.79 mL, 20.0 mmol) and DMAP (100 mg, 0.819 mmol) were added. The reaction mixture was stirred at 50 °C for 48 h. The mixture was then diluted with ethyl acetate (50 mL) and washed with 1 M hydrochloric acid solution (2 x 50 mL). The organic phases were combined, dried over anhydrous MgSO$_4$ and concentrated *in vacuo* to afford N-benzhydrylformamide as a white solid (2.10 g, 99%), which was used without further purification.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.27 (1H, s), 7.39-7.24 (10H, m), 6.52 (1H, br s), 6.34 (1H, d, J 8.2).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 160.3, 140.9, 128.8, 127.7, 127.4, 55.7.

m.p. 132-133 °C (lit. 135 °C).
This compound was prepared according to general procedure A, using N-benzhydrylformamide (1.00 g, 4.74 mmol). Column chromatography (petrol:ethyl acetate [19:1]) afforded the title compound as a white solid (871 mg, 95%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45-7.34 (10H, m), 5.94 (1H, s).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 158.3, 137.6, 129.0, 128.5, 126.6, 62.0 (t, $J$ 6.6).

m.p. 46-47 °C.


4,4'-((Isocyanomethylene)bis(methylbenzene)
the reaction was stirred at 170 °C for 12 h. The reaction mixture was then allowed to cool to room temperature and dissolved in ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo. Recrystallisation from chloroform/hexanes afforded \( N\)-(di-\( p\)-tolylmethyl)formamide as a colourless solid (5.57 g, 98%).

\(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 8.22 (1H, s), 7.21-7.11 (8H, m), 6.62 (1H, d, \( J \) 7.7, NH), 6.25 (1H, d, \( J \) 8.3), 2.36 (6H, s).

\(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta \) 160.3, 138.3, 137.2, 129.4, 127.3, 55.2, 21.1.

m.p. 117-118 °C (lit. 113-114 °C).


This compound was prepared according to general procedure A, using \( N\)-(di-\( p\)-tolylmethyl)formamide (1.00 g, 4.18 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded the title compound as a white solid (630 mg, 68%).

\(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 7.23 (4H, d, \( J \) 8.0), 7.16 (4H, d, \( J \) 8.0), 5.83 (1H, s), 2.33 (6H, s).

\(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta \) 157.8, 138.3, 135.0, 129.6, 126.5, 61.6 (t, \( J \) 6.3), 21.1.

m.p. 53-54 °C (lit. 57-58 °C).

**4,4’-(Isocyanomethylene)bis(chlorobenzene)**

To a solution of bis(4-chlorophenyl)methanone (5.00 g, 19.9 mmol) in formamide (3.95 mL, 99.5 mmol), formic acid (938 µL, 24.9 mmol) was added, and the reaction was stirred at 170 °C for 12 h. The reaction mixture was then allowed to cool to room temperature and dissolved in ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. Recrystallisation from chloroform/hexanes afforded *N*-((bis(4-chlorophenyl)methyl)formamide as a colourless solid (3.85 g, 69%).

**¹H NMR (400 MHz, DMSO-d₆)** δ 9.17 (1H, d, J 8.5, NH), 8.19 (1H, s), 7.42 (4H, d, J 8.4), 7.32 (4H, d, J 8.4), 6.23 (1H, d, J 8.7).

**¹³C NMR (101 MHz, DMSO-d₆)** δ 160.8, 141.2, 132.4, 129.5, 129.0, 53.8.

m.p. 129-131 °C (lit. 125-126 °C).


This compound was prepared according to general procedure A, using *N*-((bis(4-chlorophenyl)methyl)formamide (1.00 g, 3.57 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded the title
compound as a white solid (851 mg, 91%).

IR (neat) $v_{\text{max}}$ 2974, 2151, 1128, 875 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36 (4H, d, $J$ 8.4), 7.27 (4H, d, $J$ 8.4), 5.86 (1H, s).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 159.5, 135.6, 134.8, 129.3, 128.0, 60.7 (t, $J$ 5.1).

$m/z$ HRMS (ESI$^+$) 284.0012 ([M+Na]$^+$, C$_{14}$H$_9$Cl$_2$NNa requires 284.0004).

m.p. 78-81 °C.

9-Isocyno-9H-fluorene

To a solution of 9-fluorenone (5.00 g, 27.7 mmol) in formamide (11.0 mL, 227 mmol), formic acid (1.31 mL, 34.7 mmol) was added, and the reaction was stirred at 170 °C for 12 h. The reaction was then removed from the heat source and solidified after 1 minute. The resulting solid was dissolved in hot ethyl acetate (500 mL), washed with brine (2 x 100 mL), dried over anhydrous MgSO$_4$ and concentrated in vacuo. Recrystallisation from ethyl acetate afforded N-(9H-fluoren-9-yl)formamide as a white solid (2.03 g, 35%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.51 (1H, s), 7.71 (2H, d, $J$ 7.5), 7.59 (2H, dd, $J$ 7.4, 0.6), 7.43 (2H, t, $J$ 7.4), 7.34 (2H, td, $J$ 7.4, 1.1), 6.30 (1H, d, $J$ 9.0), 5.88 (1H, br s).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.7, 143.7, 140.7, 128.9, 127.9, 125.1, 120.1, 53.3.
m.p. 191-194 °C (lit. 209 °C).


To a solution of N-(9H-fluoren-9-yl)formamide (350 mg, 1.67 mmol) in THF (2 mL) at -78 °C, triethylamine (1.2 mL, 8.37 mmol) was added, followed by POCl₃ (172 µL, 1.85 mmol) as a solution in THF (2 mL). The reaction mixture was allowed to warm to RT and stirred for 1 h, before ice water (40 mL) was added. The reaction was then extracted into ether, washed with brine, dried over anhydrous Na₂SO₄ and concentrated in vacuo. Column chromatography (petrol:ethyl acetate [9:1]) afforded the title compound as a yellow solid (275 mg, 86%).

¹H NMR (400 MHz, CDCl₃) δ 7.74-7.70 (4H, m), 7.49 (2H, t, J 7.4), 7.41 (2H, td, J 7.5, 1.0), 5.64 (1H, s).

¹³C NMR (101 MHz, CDCl₃) δ 157.8, 140.2, 139.6, 129.8, 128.3, 124.9, 120.4, 56.8 (t, J 6.8).

m.p. 92-94 °C (lit. 87-91 °C).


Methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanooacetate (23)
Prepared according to general procedure B using methyl 2-isocyanoacetate (832 µL, 9.15 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 23 as yellow oil (1.35 g, 62%).

$\nu_{\text{max}}$ (neat): 2960, 2148, 1758, 1594, 1532, 1348, 1231, 752 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.37-8.28 (1H, m), 7.65-7.57 (1H, m), 7.34 (1H, ddd, J 12.3, 7.5, 4.1), 6.44 (1H, s), 3.89 (3H, s).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.8, 164.2, 164.1, 143.0, 130.3 (d, J 9.0), 128.9 (d, J 10.0), 117.6 (d, J 23.0), 116.9 (d, J 26.3), 57.3, 54.4.

$^{19}$F NMR (377 MHz, CDCl$_3$, $^1$H) $\delta$ -99.5.

HRMS (ESI): found 261.0270; C$_{10}$H$_7$FN$_2$NaO$_4$ [M+Na$^+$] requires 261.0282.

**Methyl 2-isocyano-3-methylbutanoate**

\[
\begin{align*}
\text{MeOOC} & \quad \text{NH}_2\text{HCl} \\
\text{MeOOC} & \quad \text{NC}
\end{align*}
\]

Prepared according to general procedure C using valine methyl ester hydrochloride (1.00 g, 5.95 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound as a colourless oil (570 mg, 68%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.12 (1H, d, J 4.2), 3.76 (3H, s), 2.35-2.19 (1H, m), 1.04 (3H, d, J 6.8), 0.94 (3H, d, J 6.7).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.9, 160.5, 62.9, 53.2, 31.2, 19.3, 16.7.

Methyl 2-isocyno-3-phenylpropanoate

\[
\text{MeOOC} - \text{Ph} - \text{NH}_2\text{HCl} \rightarrow \text{MeOOC} - \text{Ph} - \text{NC}
\]

Prepared according to general procedure C using phenylalanine methyl ester hydrochloride (910 mg, 4.21 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound as a colourless oil (581 mg, 73%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.31-7.15 (5H, m), 4.39 (1H, dd, \(J\) 8.3, 4.8), 3.72 (3H, s), 3.19 (1H, dd, \(J\) 13.9, 4.8), 3.07 (1H, dd, \(J\) 13.8, 8.4).

\(^1^3\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 166.6, 161.0, 134.4, 129.3, 128.9, 127.9, 58.0, 53.4, 38.9.


Methyl 2-isocyno-2-(5-methyl-2-nitrophenyl)acetate

\[
\text{CN} - \text{CO}_2\text{Me} \rightarrow \text{Ar-F}
\]
Prepared according to general procedure B using methyl 2-isocyanoacetate (909 µL, 10.0 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded the title compound as yellow oil (1.51 g, 65 % yield).

\[ \text{Me} \begin{array}{c} \text{NO}_2 \\ \text{CN} \end{array} \text{CO}_2\text{Me} \]

\[ 1^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta 8.14 (1H, d, J 8.4), 7.64 (1H, s), 7.44 (1H, dd, J 8.4, 1.0), 6.41 (1H, s), 3.86 (3H, s), 2.56 (3H, s). \]

\[ 13^1\text{C NMR (101 MHz, CDCl}_3\text{) } \delta 164.8, 162.9, 146.3, 144.7, 131.1, 129.8, 126.7, 126.0, 57.3, 54.1, 21.7. \]

\[ \nu_{\text{max}} \text{ (neat): 2977, 2154, 1729, 1589, 1538, 1354, 1231, 827 cm}^{-1}. \]

HRMS (ESI): found 257.0538; \( \text{C}_{11}\text{H}_{10}\text{N}_2\text{NaO}_4 \ [\text{M+Na}^+] \) requires 257.0533.

**Methyl 2-isocyno-2-(2-(trifluoromethyl)phenyl)acetate**

\[ \text{NH}_2 \begin{array}{c} \text{CF}_3 \\ \text{NH} \end{array} \text{CO}_2\text{Me} \]

To a solution of (2-(trifluoromethyl)phenyl)methanamine (1.20 g, 6.85 mmol) in ethyl formate (5.0 mL), triethylamine (1.10 mL, 7.54 mmol) was added, and the reaction mixture was stirred and heated to reflux for 48 h. The mixture was then allowed to cool to room temperature and concentrated in vacuo. Column chromatography (petrol:ethyl acetate [1:1]) afforded N-(2-(trifluoromethyl)benzyl)formamide as a colourless oil (715 mg, 51%).

\[ 1^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta 8.27 (1H, s), 7.67 (1H, d, J 7.9), 7.62-7.52 (2H, m), 7.42 (1H, t, J 7.4), 6.19 (1H, br s), 4.67 (2H, d, J 6.2). \]
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 161.1, 136.0 (q, J 2.5), 132.4, 130.9, 128.2 (q, J 30.4), 127.8, 126.0 (q, J 5.7), 124.5 (q, J 273.1), 38.7 (q, J 2.1).

$^{19}$F NMR (377 MHz, CDCl$_3$) δ -59.4 (m).


To a solution of N-(2-(trifluoromethyl)benzyl)formamide (700 mg, 3.29 mmol) in DCM (4 mL) at 0 °C, Et$_3$N (1.14 mL, 8.22 mmol) was added, and then POCl$_3$ (307 µL, 3.29 mmol) dropwise. The reaction was stirred for 90 min. Saturated sodium carbonate solution (5 mL) was then added and stirring was continued for 30 min, before water (8 mL) was added. The aqueous phase was extracted with DCM and the combined organic extracts were washed with brine, dried over anhydrous MgSO$_4$ and concentrated in vacuo. The crude residue was then dissolved in THF (10 mL) and cooled to -78 °C, before the dropwise addition of LiHMDS (1.21 g, 7.24 mmol) in toluene (7.2 mL). The reaction mixture was left to stir at -78 °C for 1h, after which dimethyl carbonate (332 µL, 3.95 mmol) was added and the reaction was allowed to warm to room temperature. The crude mixture was concentrated in vacuo, before the residue was diluted with ethyl acetate (35 mL) and washed with saturated aqueous ammonium chloride solution (35 mL), brine (35 mL) and water (35 mL). The organic phases were combined, dried over anhydrous MgSO$_4$ and concentrated in vacuo. Column chromatography (petrol:ethyl acetate [9:1]) afforded the title compound as a brown oil (267 mg, 33%).

IR (neat) $\nu_{\text{max}}$ 3025, 2157, 1612, 1487, 1046 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.79 (1H, d, J 7.6), 7.77 (1H, d, J 7.6), 7.71 (1H, t, J 7.6), 7.59 (1H, t, J 7.6), 5.78 (1H, s), 3.84 (3H, s).
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 165.5, 161.6, 133.1, 130.8, 130.0, 129.1, 128.2 (q, $J$ 31.3), 126.5 (q, $J$ 5.4), 123.6 (q, $J$ 273.2), 55.8, 54.0.

$^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ -58.4 (m).

$m/z$ HRMS (ESI$^+$) 266.0398 ([M+Na]$^+$, C$_{11}$H$_8$F$_3$NO$_2$Na requires 266.0399).

**Methyl 2-isocyano-2-(2-methoxyphenyl)acetate**

![Methyl 2-isocyano-2-(2-methoxyphenyl)acetate](image)

(2-Methoxyphenyl)methanamine (1.31 mL, 10.0 mmol) was dissolved in formic acid (20 mL) at room temperature. Acetic anhydride (1.42 mL, 15.0 mmol) was added dropwise over 2 h, and the mixture was stirred for 16 h. The crude mixture was concentrated *in vacuo*, and the residue was then dissolved in ethyl acetate (20 mL) and filtered through a short silica column. Under an atmosphere of argon, the mixture was dissolved in THF (20 mL) and cooled to 0 °C. Triethylamine (7.00 mL, 50.0 mmol) was added, and then POCl$_3$ (1.40 mL, 15.0 mmol) was added dropwise over 10 min. The reaction mixture left to stir at 0 °C. After 2 h, the reaction was quenched with 10% aqueous sodium carbonate solution, and stirred for a further 10 min. The mixture was concentrated *in vacuo*, before column chromatography (petrol:ethyl acetate [8:1]) afforded 1-(isocyanomethyl)-2-methoxybenzene as a colourless oil (1.07 g, 73%).

IR (neat) $\nu_{\text{max}}$ 2150, 1604, 1495, 1464, 1249, 1113, 1027 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46 (1H, d, $J$ 7.5), 7.41-7.35 (1H, m), 7.05 (1H, app. t, $J$ 7.5), 6.93 (1H, d, $J$ 8.2), 4.66 (2H, s), 3.88 (3H, s).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 157.1, 156.3, 129.7, 127.7, 120.8, 120.7, 110.3, 55.4, 41.2.

HRMS (ESI$^+$) 170.0575 ([M+Na]$^+$, C$_9$H$_9$NONa requires 170.0582).

1-(Isocyanomethyl)-2-methoxybenzene (200 mg, 1.36 mmol) was dissolved in THF (5.5 mL) at -78 °C. LiHMDS (502 mg, 3.00 mmol) in THF (3.0 mL) was added dropwise over 10 min, and the reaction mixture was left to stir at -78 °C. After 1 h dimethyl carbonate (137 μL, 1.63 mmol) was added, and the reaction was allowed to warm to room temperature. The crude mixture was concentrated in vacuo, before the residue was diluted with ethyl acetate (15 mL) and washed with saturated aqueous ammonium chloride solution (15 mL), brine (15 mL) and water (15 mL). The organic phases were combined, dried over anhydrous MgSO$_4$ and concentrated in vacuo. Column chromatography (petrol:ethyl acetate [5:1]) afforded the title compound as a light yellow oil (170 mg, 61%).

IR (neat) $\nu_{\text{max}}$ 3027, 2151, 1602, 1495, 1030, 726 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.47-7.37 (2H, m), 7.04 (1H, app. t, $J$ 7.5), 6.96 (1H, d, $J$ 8.3), 5.76 (1H, s), 3.89 (3H, s), 3.80 (3H, s).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 166.4, 159.7, 156.2, 131.4, 128.3, 121.2, 121.1, 111.3, 55.9, 54.8, 53.6.

HRMS (ESI$^+$) 228.0630 ([M+Na]$^+$, C$_{11}$H$_{11}$NO$_3$Na requires 228.0637).

Methyl 2-isocyano-2-(2-nitrophenyl)acetate

\[
\begin{align*}
\text{CN} & \text{CO}_2\text{Me} \quad \text{Ar-F} \\
\text{CN} & \text{CO}_2\text{Me}
\end{align*}
\]
Prepared according to general procedure B, using 1-fluoro-2-nitrobenzene (1.37 mL, 13.0 mmol). Column chromatography (petrol:ethyl acetate [17:3]) afforded the title compound as a brown oil (1.29 g, 58%).

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3\text{) } & \delta 8.23 (1H, dd, J 8.2, 1.2), 7.89 (1H, dd, J 7.8, 1.4), 7.83 (1H, td, J 7.8, 1.3), 7.68 (1H, ddd, J 8.1, 7.5, 1.5), 6.42 (1H, s), 3.87 (3H, s). \\
\text{C NMR (101 MHz, CDCl}_3\text{) } & \delta 164.7, 163.2, 147.0, 134.6, 130.7, 129.3, 126.8, 125.8, 57.2, 54.2.
\end{align*}
\]


Benzyl 2-(5-fluoro-2-nitrophenyl)-2-isocynoacetate

\[
\begin{align*}
\text{To a suspension of glycine (1.20 g, 16.0 mmol) in benzyl alcohol (32 mL), tosylic acid (2.74 g, 16.0 mmol) was added. The reaction was stirred at 80 } \degree \text{C, before tosyl chloride (3.43 g, 18.0 mmol) was added portionwise. Stirring was continued at 80 } \degree \text{C for 2 h before cooling to room temperature. Ether was then carefully added until precipitation was witnessed, at which point the flask was placed in a freezer for 24 h. The resultant solid was filtered and recrystallised from ethanol/ether to afford 2-(benzyloxy)-2-oxoethanaminium tosylate as a white solid (2.24 g, 41%).}
\end{align*}
\]
$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.26 (3H, br s), 7.50 (2H, d, $J$ 7.8), 7.46-7.35 (5H, m), 7.13 (2H, d, $J$ 7.8), 5.25 (2H, s), 3.92 (2H, s), 2.30 (3H, s).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 168.1, 146.1, 138.2, 135.7, 129.0, 128.9, 128.7, 128.6, 126.0, 67.3, 40.2, 21.3.

m.p. 132-133 °C (lit. 131-133 °C).


To a suspension of 2-(benzyloxy)-2-oxoethanaminium tosylate (930 mg, 2.76 mmol) in ethyl formate (2.5 mL), triethylamine (423 $\mu$L, 3.03 mmol) was added, and the reaction mixture was stirred and heated to reflux for 48 h. The mixture was then allowed to cool to room temperature and concentrated in vacuo. Column chromatography (petrol:ethyl acetate [1:1]) afforded benzyl 2-formamidoacetate as a colourless oil (416 mg, 78%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.26 (1H, s), 7.42-7.34 (5H, m), 6.39 (1H, br s), 5.23 (2H, s), 4.15 (2H, d, $J$ 5.4).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.4, 161.2, 135.0, 128.7, 128.5, 67.4, 40.0.


Prepared according to general procedure A using benzyl 2-formamidoacetate (400 mg, 2.07 mmol). The crude compound (368 mg,
99%) was used without further purification.

^1^H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.42-7.36 (5H, m), 5.26 (2H, s), 4.27 (2H, s).

^1^3^C NMR (101 MHz, CDCl\textsubscript{3}) δ 163.8, 161.6, 134.4, 129.0, 128.8, 128.7, 68.4, 43.6.


Prepared according to general procedure B using benzyl 2-isocyanatoacetate (365 mg, 2.08 mmol). Column chromatography (petrol:ethyl acetate [17:3]) afforded the title compound as a brown oil (430 mg, 66%).

IR (neat) ν\textsubscript{max} 3006, 2152, 1594, 1342, 1277, 1210, 978 cm\textsuperscript{-1}.

^1^H NMR (400 MHz, CDCl\textsubscript{3}) δ 8.29 (1H, dd, J 9.2, 5.0), 7.57 (1H, dd, J 8.7, 2.7), 7.41-7.28 (6H, m), 6.45 (1H, s), 5.26 (2H, s).

^1^3^C NMR (101 MHz, CDCl\textsubscript{3}) δ 164.8 (d, J 261.0), 164.1, 164.1 (d, J 2.0), 163.4, 134.0, 130.3 (d, J 9.1), 129.0, 128.9 (d, J 10.3), 128.8, 128.4, 117.5 (d, J 23.0), 116.8 (d, J 26.0), 69.4, 57.5.

^1^9^F NMR (377 MHz, CDCl\textsubscript{3}, ^1^H) δ -99.6.

m/z HRMS (ESI^+) 337.0599 ([M+Na]^+) requires 337.0595).

Isopropyl 2-(5-flouro-2-nitrophenyl)-2-isocyanatoacetate

\[
\begin{align*}
\text{H}_2\text{N} & \overset{\text{CO}_2\text{H}}{\rightleftharpoons} \text{H} \overset{\text{N}}{\overset{\text{NH}}{\overset{\text{O}}{\overset{\text{O}}{\overset{\text{F}}{\overset{\text{NO}_2}{\overset{\text{CN}}{\overset{\text{CO}_2\text{Pr}}{\rightarrow}}}}}}}}
\end{align*}
\]
To a solution of glycine (2.40 g, 32.0 mmol) in isopropyl alcohol (50 mL), thionyl chloride (4.60 mL, 64.0 mmol) was added, and the reaction was heated at reflux for 12 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo to furnish a sticky oil. The crude residue was suspended in ethyl formate (21 mL), and triethylamine (4.9 mL, 35.0 mmol) was then added. The reaction was heated at reflux for 48 h, before cooling to room temperature and concentrating in vacuo. Column chromatography (petrol:ethyl acetate [1:1]) afforded isopropyl 2-formamidoacetate as a colourless oil (4.07 g, 88%).

IR (neat) $\nu_{\text{max}}$ 3348, 2989, 1726, 1579, 1202, 1116, 1037 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.23 (1H, s), 6.48 (1H, br s), 5.06 (1H, sept, $J$ 6.3), 4.02 (2H, dd, $J$ 5.4, 0.8), 1.25 (6H, d, $J$ 6.3).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.1, 161.2, 69.6, 40.2, 21.7.

$m/z$ HRMS (ESI$^+$) 168.0639 ([M+Na]$^+$, $C_6H_{11}$F$_3$NO$_3$Na requires 168.0631).

To a solution of isopropyl 2-formamidoacetate (2.00 g, 13.8 mmol) in DCM (15 mL) at 0 °C, triethylamine (4.90 mL, 34.5 mmol) was added, and then POCl$_3$ (1.29 mL, 13.8 mmol) dropwise. The reaction mixture was stirred for 90 min. Saturated sodium carbonate solution (21 mL) was then added and stirring was continued for 30 min, before water (35 mL) was added. The aqueous phase was extracted with DCM and the combined organic extracts were washed with brine, dried over anhydrous MgSO$_4$ and concentrated in vacuo. The crude residue was then dissolved in DMSO (70 mL) at room temperature. Cesium carbonate (6.7 g, 20.7 mmol) was added, and the mixture was stirred for 10 min. 2,4-Difluoronitrobenzene (1.97 mL, 18.0 mmol) was added dropwise, and the reaction was stirred for 24 hours. The mixture was then diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic phases were combined, dried over anhydrous MgSO$_4$
and concentrated in vacuo, before column chromatography (petrol:ethyl acetate [9:1]) afforded isopropyl isocyanoacetate as a brown oil (808 mg, 22%).

IR (neat) $\nu_{\text{max}}$ 2981, 2152, 1778, 1591, 1541, 1345, 1229, 857 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.28 (1H, dd, $J$ 9.2, 5.0), 7.59 (1H, dd, $J$ 8.9, 2.8), 7.31 (1H, ddd, $J$ 9.1, 6.9, 2.7), 6.36 (1H, s), 5.09 (1H, sept, $J$ 6.2), 1.31 (3H, d, $J$ 6.2), 1.27 (3H, d, $J$ 6.2).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 165.4 (d, $J$ 260.4), 163.8, 163.0, 130.5 (d, $J$ 9.1), 128.8 (d, $J$ 9.9), 117.4 (d, $J$ 22.7), 116.7 (d, $J$ 26.3), 72.4, 57.8, 21.4, 21.3.

$^{19}$F NMR (377 MHz, CDCl$_3$, $^1$H) $\delta$ -99.5.

$m/z$ HRMS (ESI$^+$) 289.0598 ([M+Na]$^+$, C$_{12}$H$_{11}$FN$_2$O$_4$Na requires 289.0595).

Methyl 2-{4-chloro-2-nitrophenyl}-2-isocyanoacetate

![Chemical structure](image)

This compound was prepared according to general procedure B, using 5-chloro-2-fluoronitrotoluene (1.53 mL, 13.0 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded the title compound as a brown oil (1.78 g, 70%).

IR (neat) $\nu_{\text{max}}$ 2992, 2156, 1612, 1337, 1237, 1219, 827 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.21 (1H, d, $J$ 2.0), 7.84 (1H, d, $J$ 8.4), 7.79 (1H, dd, $J$ 8.4, 2.1), 6.38 (1H, s), 3.87 (3H, s).
\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.3, 163.8, 147.3, 136.8, 134.5, 130.4, 126.0, 125.2, 56.8, 54.4.

\(m/z\) HRMS (ESI\(^+\)) 276.9990 ([M+Na]\(^+\), \(C_{10}H_7ClN_2O_4Na\) requires 276.9987).

Methyl 2-(3-fluoro-2-nitrophenyl)-2-isocyanocacetate

This compound was prepared according to general procedure B, using 2,6-difluoronitrobenzene (2.07 g, 13.0 mmol). Column chromatography (petrol:ethyl acetate [6:1]) afforded the title compound as a brown oil (1.65 g, 69\%).

IR (neat) \(\nu_{\text{max}}\), 3001, 2146, 1589, 1335, 1256, 1222 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.70 (1H, td, \(J\) 8.2, 5.1), 7.62 (1H, d, \(J\) 8.0), 7.43 (1H, ddd, \(J\) 9.4, 8.5, 1.2), 6.01 (1H, s), 3.85 (3H, s).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 164.0, 164.0, 154.9 (d, \(J\) 262.2), 141.6, 133.6 (d, \(J\) 8.8), 127.0, 123.7 (d, \(J\) 3.8), 119.1 (d, \(J\) 20.0), 55.6, 54.4.

\(^{19}\)F NMR (377 MHz, CDCl\(_3\), \{\(^1\)H\}) \(\delta\) -119.0.

\(m/z\) HRMS (ESI\(^+\)) 261.0290 ([M+Na]\(^+\), \(C_{10}H_7FN_2O_4Na\) requires 261.0282).

Methyl 2-isocynano-2-(4-methyl-2-nitrophenyl)acacetate
This compound was prepared according to general procedure B, using 4-fluoro-3-nitrotoluene (2.02 g, 13.0 mmol). Column chromatography (petrol:ethyl acetate [9:1]) afforded the title compound as a brown oil (1.46 g, 60%).

IR (neat) ν_{max} 2962, 2150, 1527, 1355, 1257, 1231, 989 cm^{-1}.

¹H NMR (400 MHz, CDCl₃) δ 8.00 (1H, s), 7.71 (1H, d, J = 8.0), 7.60 (1H, dd, J = 8.0, 0.8), 6.31 (1H, s), 3.83 (3H, s), 2.51 (3H, s).

¹³C NMR (101 MHz, CDCl₃) δ 164.9, 162.8, 146.8, 141.6, 135.2, 129.2, 126.2, 123.9, 57.1, 54.1, 21.0.

m/z HRMS (ESI⁺) 257.0535 ([M+Na]⁺, C_{11}H_{10}N_{2}O_{4}Na requires 257.0533).
2.2 Synthesis of Michael Acceptors

**General Procedure D:** Zinc dust (10 eq) and ammonium chloride (15 eq) were added to a vigorously stirred room temperature solution of the relevant isopropyl acrylate (1.0 eq) in acetone:water [4:1] (5.0 mL/mmole substrate). After 15 min the reaction mixture was decanted from the remaining zinc residue; the residue was washed with ethyl acetate (2 x 5.0 mL/mmole substrate) and the washings were decanted and combined. The combined organic phases were filtered through Celite®, washed with water (5.0 mL/mmole substrate), dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The crude residue was then dissolved in chloroform (3.0 mL/mmole substrate); pyridine (1.3 eq) was added, and the solution was cooled to 0 °C and stirred. Ethyl chloroformate (1.2 eq) was added dropwise into the reaction mixture. The mixture was stirred for 3 h and allowed to warm to room temperature. The solution was then washed with brine (2.0 mL/mmole substrate) and water (2 x 2.0 mL/mmole substrate), dried over anhydrous MgSO₄ and concentrated in vacuo.

**General Procedure E:** Potassium carbonate (1.0 eq) and diisopropyl malonate (1.0 eq) were dissolved in DMF (1.7 mL/mmole substrate), and stirred for 10 min at 90 °C. After allowing the reaction mixture to cool to room temperature, the relevant 2-fluoronitrobenzene (1.0 eq) was added, and then stirred for 3 h at 90 °C. After cooling to room temperature, the reaction mixture was diluted with 5% aqueous hydrochloric acid solution (2.5 mL/mmole substrate) and extracted with diethyl ether (3 x 5.0 mL/mmole substrate). The organic phases were combined, washed with brine (5.0 mL/mmole substrate) and water (5.0 mL/mmole substrate), dried over anhydrous MgSO₄ and concentrated in vacuo. The crude residue was then dissolved in DMSO (1.7 mL/mmole substrate), before sodium chloride (1.0 eq) and water (2.0 eq) were added. The reaction mixture was stirred for 24 h at 130 °C. After cooling to room temperature, the mixture was diluted with water (2.5
mL/mmole substrate) and extracted with ethyl acetate (3 x 5.0 mL/mmole substrate). The organic phases were then combined, washed with brine (5.0 mL/mmole substrate) and water (5.0 mL/mmole substrate), dried over anhydrous MgSO₄ and concentrated *in vacuo*.

**General Procedure F:** Paraformaldehyde (2.80 eq), tetrabutylammonium bromide (0.04 eq) and potassium carbonate (3.00 eq) were added to a stirred solution of the relevant isopropyl acetate (1.00 eq) in toluene (1.5 mL/mmole substrate), and the solution was heated to 50 °C. After 20 h the solution was allowed to cool to room temperature, water (3.5 mL/mmole substrate) was added and the aqueous layer was extracted with toluene (3 x 2.0 mL/mmole). The combined organic fractions were dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*.

**Isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (1)**

![Chemical structure of Isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate](image)

Concentrated sulfuric acid (5.0 mL) was added to a stirred solution of 2-nitrophenylacetic acid (15.0 g, 82.8 mmol) in isopropanol (50 mL) at room temperature. The mixture was then stirred at reflux for 4 h. After allowing to cool to room temperature, EtOAc (200 mL) was added. The mixture was washed with water (100 mL) and then with saturated aqueous sodium bicarbonate solution (2 x 100 mL). The combined organic phases were dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to afford isopropyl 2-(2-nitrophenyl)acetate as an orange oil (17.2 g, 93%), which was used without further purification.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.07 (1H, d, $J$ 8.1), 7.57 (1H, app. t, $J$ 7.5), 7.49-7.41 (1H, m), 7.33 (1H, d, $J$ 7.5), 5.01 (1H, sept, $J$ 6.2), 3.97 (2H, s), 1.21 (6H, d, $J$ 6.2).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.4, 148.8, 133.5, 133.3, 130.0, 128.5, 125.2, 68.8, 40.1, 21.7.


Prepared from isopropyl 2-(2-nitrophenyl)acetate (16.0 g) according to general procedure F to afford isopropyl 2-(2-nitrophenyl)acrylate as an orange oil (15.0 g, 89%), which was used without further purification.

IR (neat) $\nu_{\text{max}}$ 3071, 2983, 2937, 1716, 1526, 1350, 1207 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.11 (1H, d, $J$ 8.1), 7.65 (1H, app. td, $J$ 7.5, 1.5), 7.58-7.46 (1H, m), 7.39 (1H, dd, $J$ 7.4, 1.5), 6.53 (1H, d, $J$ 1.0), 5.86 (1H, d, $J$ 1.0), 5.05 (1H, sept, $J$ 6.2), 1.21 (6H, d, $J$ 6.2).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 164.2, 148.0, 140.5, 133.6, 133.2, 132.1, 129.2, 127.1, 124.5, 69.2, 21.5.

HRMS (ESI$^+$) 258.0747 ([M+Na]$^+$, C$_{12}$H$_{13}$NO$_4$Na requires 258.0742).

This compound was prepared according to general procedure D, using ethyl chloroformate (2.70 mL, 28.1 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 1 as an orange wax (3.61 g, 56%).

IR (neat) $\nu_{\text{max}}$ 3343, 2982, 1806, 1714, 1583, 1521, 1451, 1299, 1211, 1105, 1059 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.88 (1H, app. s), 7.41-7.35 (1H, m), 7.20-7.09 (2H, m), 6.93 (1H, br s, NH), 6.57 (1H, d, $J$ 1.5), 5.85 (1H, d, $J$ 1.5), 5.15 (1H, sept, $J$ 6.2), 4.21 (2H, q, $J$ 7.1), 1.34-1.28 (9H, m).
\[ ^{13}\text{C} \text{ NMR (101 MHz, CDCl}_3 \} \delta 166.2, 153.9, 139.8, 135.4, 130.5, 130.2, 129.2, 126.9, 124.0, 121.9, 69.3, 61.2, 21.7, 14.6. \]

HRMS (ESI') 300.1208 ([M+Na]\(^{+}\), \(C_{15}H_{19}NO_4\)Na requires 300.1212).

m.p. 45-47 °C.

**Isopropyl 2-(2-(((benzyl)oxy)carbonyl)amino)phenyl)acrylate**

This compound was prepared according to general procedure D, using benzyl chloroformate (1.46 mL, 10.2 mmol). Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound as an orange solid (1.53 g, 53%).

IR (neat) \( \nu_{\max} \) 3340, 2981, 1712, 1584, 1519, 1451, 1298, 1199, 1105, 1042, 937, 817 cm\(^{-1}\).

\(^1\text{H} \text{ NMR (400 MHz, CDCl}_3 \} \delta 7.97-7.84 (1H, \text{ m}), 7.50-7.30 (6H, \text{ m}), 7.21-7.11 (2H, \text{ m}), 7.06 (1H, \text{ br s, NH}), 6.56 (1H, \text{ d, } J 1.4), 5.85 (1H, \text{ d, } J 1.4), 5.21 (2H, \text{ s}), 5.12 (1H, \text{ sept, } J 6.3), 1.27 (6H, \text{ d, } J 6.3). \)

\[ ^{13}\text{C} \text{ NMR (101 MHz, CDCl}_3 \} \delta 166.2, 153.8, 139.7, 136.2, 135.3, 130.6, 130.3, 129.2, 128.9, 128.6, 128.4, 128.3, 124.1, 122.1, 69.3, 67.0, 21.7. \]

HRMS (ESI') 362.1356 ([M+Na]\(^{+}\), \(C_{20}H_{21}NO_4\)Na requires 362.1368).

m.p. 52-58 °C.
Isopropyl 2-(4-acetyl-2-((ethoxycarbonyl)amino)phenyl)acrylate

This compound was prepared according to general procedure E, using 4'-fluoro-3'-nitroacetophenone (4.00 g, 21.8 mmol). Column chromatography (petrol:ethyl acetate [5:1]) afforded isopropyl 2-(4-acetyl-2-nitrophenyl)acetate as a yellow solid (3.01 g, 52%).

IR (neat) $\nu_{\text{max}}$ 2983, 1729, 1692, 1619, 1534, 1354, 1254, 1219, 1105 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.64 (1H, d, $J$ 1.7), 8.16 (1H, dd, $J$ 7.9, 1.7), 7.50 (1H, d, $J$ 7.9), 5.04 (1H, sept, $J$ 6.3), 4.06 (2H, s), 2.68 (3H, s), 1.24 (6H, d, $J$ 6.3).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 195.4, 168.7, 149.0, 137.3, 133.9, 132.4, 132.0, 125.0, 69.3, 40.1, 26.7, 21.7.

HRMS (ESI$^+$) 288.0853 ([M+Na]$^+$, C$_{13}$H$_{15}$NO$_5$Na requires 288.0842).

m.p. 47-49 °C.

This compound was prepared according to general procedure F, using isopropyl 2-(4-acetyl-2-nitrophenyl)acetate (2.20 g, 8.29 mmol). Column chromatography (petrol:ethyl acetate [3:1]) afforded isopropyl 2-(4-acetyl-2-nitrophenyl)acrylate as a yellow oil (529 mg, 23%).

IR (neat) $\nu_{\text{max}}$ 3049, 2916, 1736, 1713, 1619, 1499, 1265 cm$^{-1}$.
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.62 (1H, s), 8.20 (1H, d, J 8.0), 7.52 (1H, d, J 8.0), 6.59 (1H, app. s), 5.93 (1H, app. s), 5.04 (1H, sept, J 6.2), 2.68 (3H, s), 1.20 (6H, d, J 6.2).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 195.4, 163.6, 148.2, 139.8, 137.8, 137.1, 132.7, 132.6, 128.2, 124.3, 69.6, 26.7, 21.5.

HRMS (ESI$^+$) 300.0846 ([M+Na]$^+$, C$_{14}$H$_{15}$NO$_5$Na requires 300.0848).

This compound was prepared according to general procedure D, using isopropyl 2-(4-acetyl-2-nitrophenyl)acrylate (500 mg, 1.80 mmol). Column chromatography (petrol:ethyl acetate [3:1]) afforded the title compound as a yellow oil (172 mg, 30%).

IR (neat) $\nu_{max}$ 3322, 2982, 1716, 1686, 1572, 1525, 1422, 1290, 1211, 1096, 1054 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.41 (1H, s), 7.63 (1H, dd, J 7.9, 1.7), 7.17 (1H, d, J 7.9), 6.89 (1H, br s, NH), 6.54 (1H, app. s), 5.79 (1H, app. s), 5.06 (1H, sept, J 6.2), 4.14 (2H, q, J 7.1), 2.55 (3H, s), 1.26-1.18 (9H, m).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 197.6, 165.6, 153.8, 139.1, 137.8, 135.9, 131.3, 130.6, 125.3, 123.3, 122.1, 69.6, 61.5, 26.8, 21.7, 14.5.

HRMS (ESI$^+$) 342.1310 ([M+Na]$^+$, C$_{17}$H$_{21}$NO$_5$Na requires 342.1317).

**Isopropyl 2-(2-((ethoxycarbonyl)amino)-4-(trifluoromethyl)phenyl)acrylate**

![Chemical structure of the compound](attachment:image.png)
This compound was prepared according to general procedure E, using 2-fluoro-5-(trifluoromethyl)nitrobenzene (1.34 mL, 9.56 mmol). Column chromatography (petrol:ethyl acetate [8:1]) afforded isopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)acetate as a yellow oil (2.17 g, 78%).

IR (neat) $\nu_{\text{max}}$ 3096, 2987, 2851, 1715, 1630, 1575, 1503 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.28 (1H, s), 7.77 (1H, d, $J$ 8.0), 7.45 (1H, d, $J$ 8.0), 4.95 (1H, sept, $J$ 6.3), 3.98 (2H, s), 1.16 (6H, d, $J$ 6.3).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.6, 148.9, 134.3, 133.9, 131.2 (q, $J$ 34.3), 129.8 (q, $J$ 3.5), 122.8 (q, $J$ 272.4, CF$_3$), 122.5 (q, $J$ 3.8), 69.4, 40.0, 21.6.

$^{19}$F NMR (377 MHz, $[^1$H], CDCl$_3$) $\delta$ -63.0.

HRMS (ESI$^+$) 314.0619 ([M+Na]$^+$, $C_{12}H_{12}F_3NO_4Na$ requires 314.0616).

This compound was prepared according to general procedure F, using isopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)acetate (2.00 g, 6.87 mmol). Isopropyl 2-(2-nitro-4-(trifluoromethyl)phenyl)acrylate was afforded as a brown oil (1.52 g, 73%), which was used without further purification.

IR (neat) $\nu_{\text{max}}$ 2940, 1714, 1541, 1352, 1134, 1087, 697 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.30 (1H, s), 7.83 (1H, app. ddd, $J$ 8.0, 1.8, 0.6), 7.49 (1H, d, $J$ 8.0), 6.54 (1H, d, $J$ 0.6), 5.86 (1H, d, $J$ 0.6), 5.03 (1H, sept, $J$ 6.3), 1.15 (6H, d, $J$ 6.3).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 163.5, 148.0, 139.5, 136.6, 133.1, 131.8 (q, $J$ 34.3), 130.1 (q, $J$ 3.5), 128.4, 122.7 (q, $J$ 272.5, CF$_3$), 121.9 (q, $J$ 3.8), 69.7, 21.5.
19F NMR (377 MHz, [1H], CDCl3) δ -62.9.

HRMS (ESI⁺) 326.0600 ([M+Na]⁺, C13H12F3NO4Na requires 326.0611).

This compound was prepared according to general procedure D, using isopropyl 2-[(2-nitro-4-(trifluoromethyl)phenyl)acrylate (1.40 g, 4.62 mmol).

Column chromatography (petrol:ethyl acetate [5:1]) afforded the title compound as a yellow oil (431 mg, 27%).

IR (neat) νmax 3341, 2985, 1719, 1584, 1534, 1471, 1333, 1214, 1127, 1095 cm⁻¹.

1H NMR (400 MHz, CDCl3) δ 8.24-8.15 (1H, m), 7.29-7.22 (1H, m), 7.20-7.14 (1H, m), 6.94 (1H, br s, NH), 6.55 (1H, d, J 1.2), 5.79 (1H, d, J 1.2), 5.06 (1H, sept, J 6.3), 4.13 (2H, q, J 7.1), 1.24-1.18 (9H, m).

13C NMR (101 MHz, CDCl3) δ 165.5, 153.6, 138.7, 138.2, 136.1, 131.6, 131.3 (q, J 32.6), 130.7, 127.9, 123.8 (q, J 272.2, CF₃), 120.2 (app. br s), 118.3 (app. br s), 69.7, 61.6 (OCH₂CH₃), 21.6, 14.5.

19F NMR (377 MHz, [1H]) δ -62.8.

HRMS (ESI⁺) 368.1086 ([M+Na]⁺, C16H18F₃NO₄Na requires 368.1068).

Isopropyl 2-(2-benzamidophenyl)acrylate

Zinc dust (5.58 g, 85.0 mmol) and ammonium chloride (6.83 g, 128 mmol) were added to a vigorously stirred room temperature solution of isopropyl 2-(2-nitrophenyl)acrylate (2.00 g, 8.50 mmol) in acetone:water [4:1] (50 mL). After 15 min the reaction mixture was decanted from the remaining zinc residue; the residue was washed with ethyl acetate (2 x 50 mL) and the washings were decanted and combined. The combined organic phases were filtered through Celite®, washed with water (50 mL), dried over
anhydrous MgSO₄, filtered and concentrated *in vacuo*. The crude residue was then dissolved in DCM (30 mL); pyridine (826 µL, 10.2 mmol) was added, and the solution was cooled to 0 °C and stirred. Benzoyl chloride (983 µL, 8.50 mmol) was added dropwise into the reaction mixture. The mixture was stirred for 12 h and allowed to warm to room temperature. The solution was then washed with brine (30 mL) and water (2 x 30 mL/mmol substrate), dried over anhydrous MgSO₄ and concentrated *in vacuo*. Column chromatography (petrol:ethyl acetate [5:1]) afforded the title compound as a light yellow solid (1.76 g, 67%).

IR (neat) ν<sub>max</sub> 3321, 2982, 1665, 1580, 1449, 1303, 1199, 1100, 1079 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.93 (1H, br s, NH), 8.06 (1H, d, J 8.0), 7.90 (2H, d, J 7.6), 7.60-7.42 (4H, m), 7.28-7.18 (2H, m) 6.54 (1H, d, J 1.3), 5.91 (1H, d, J 1.3), 5.16 (1H, sept, J 6.3), 1.30 (6H, d, J 6.3).

¹³C NMR (101 MHz, CDCl₃) δ 167.2, 165.4, 140.3, 135.3, 134.8, 131.8, 131.0, 130.6, 129.3, 128.7, 127.4, 127.1, 125.2, 124.3, 69.7, 21.7.

m/z LRMS (ESI⁺) 332.1 [M+Na]⁺; HRMS (ESI⁺) 332.1259 ([M+Na]⁺, C₁₉H₁₉NO₃Na requires 332.1263).

m.p. 75-77 °C.

**Isopropyl 2-(2-(3-(p-tolyl)ureido)phenyl)acrylate (22)**

To a solution of isopropyl 2-(2-nitrophenoxy)acrylate (4.26 g, 18.1 mmol) in acetone (80 mL) and water (20 mL) was added zinc powder (5.05 g,
77.2 mmol) followed by NH₄Cl (16.7 g, 311 mmol). The reaction was stirred vigorously for 15 minutes before the solution was decanted from the zinc residue. The residue was washed several times with EtOAc and the washings were combined and filtered through Celite. The filtrate was washed with water, dried over MgSO₄ and evaporated under reduced pressure. The crude residue was dissolved in CHCl₃ (50 mL) and 1-isocyanato-4-methylbenzene (2.28 mL, 18.1 mmol) was added. The reaction was stirred overnight and the product was filtered to afford the title compound 22 as a white solid (3.44 g, 56%).

IR (neat) νmax 3300, 3024, 1704, 1642, 1549, 1375, 1230, 1209, 1106 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.72 (1H, d, J 8.1), 7.43-7.39 (1H, m), 7.25-7.16 (4H, m), 7.15-7.08 (2H, m), 6.94 (1H, br s, NH), 6.78 (1H, br s, NH), 6.47 (1H, d, J 1.4), 5.82 (1H, d, J 1.4), 5.01 (1H, sept, J 6.2), 2.32 (3H, s), 1.22 (6H, d, J 6.2).

¹³C NMR (101 MHz) δ 166.5, 153.8, 140.1, 135.7, 135.4, 133.8, 131.9, 130.5, 129.8, 129.7, 129.4, 125.2, 125.0, 121.5, 69.4, 21.6, 20.8.

HRMS (ESI⁺) 361.1521 ([M+Na]⁺, C₂₀H₂₂N₂O₃Na requires 361.1528).

m.p. 160-165 °C.

**Isopropyl 2-(2-(3-(4-methoxyphenyl)ureido)phenyl)acrylate**
To a solution of isopropyl 2-(2-nitrophenyl)acrylate (2.35 g, 10.0 mmol) in acetone (50 mL) and water (12 mL) was added zinc powder (2.81 g, 43.0 mmol) followed by NH$_4$Cl (9.06 g, 171.0 mmol). The reaction was stirred vigorously for 15 minutes before the solution was decanted from the zinc residue. The residue was washed several times with EtOAc and the washings were combined and filtered through Celite. The filtrate was washed with water, dried over MgSO$_4$ and evaporated under reduced pressure. The crude residue was dissolved in CHCl$_3$ (25 mL) and 1-isocyanato-4-methoxybenzene (1.30 mL, 10.0 mmol) was added. The reaction was stirred overnight before concentrating in vacuo. Purification by column chromatography (petrol:ethyl acetate [3:1]) followed by recrystallisation from EtOAc/hexanes afforded the title compound as a colourless oil (1.05 g, 30%).

IR (neat) $\nu _{\text{max}}$ 3299, 3028, 1710, 1636, 1551, 1370, 1236, 1216, 1101 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.75 (1H, d, $J$ 8.0), 7.39 (1H, ddd, $J$ 7.9, 7.0, 2.2), 7.14-7.25 (4H, m), 6.94 (1H, br s, NH), 6.85 (2H, d, $J$ 8.9), 6.77 (1H, br s, NH), 6.46 (1H, d, $J$ 1.4), 5.81 (1H, d, $J$ 1.3), 5.00 (1H, sept, $J$ 6.3), 3.81 (3H, s), 1.22 (6H, d, $J$ 6.3).

$^{13}$C NMR (101 MHz) $\delta$ 166.5, 154.3, 140.1, 135.8, 133.5, 131.6, 130.7, 130.4, 129.8, 129.3, 125.0, 124.8, 124.0, 114.4, 69.4, 55.5, 21.6.

HRMS (ESI$^+$) 377.1472 ([M+Na]$^+$, $C_{20}H_{22}N_2O_4Na$ requires 377.1475).
3. Diastereoselective reaction

**General Procedure G:** The relevant Michael acceptor substrate (1.0 eq), isocyanide (1.0 eq) and tetrabutylammonium bromide (0.1 eq) were dissolved in toluene (10 mL/mmol substrate). The selected base (5.0 eq) was added, and the mixture was stirred at room temperature until both substrates were consumed according to thin layer chromatography (2-24 h). The reaction mixture was then diluted with DCM (20 mL/mmol substrate) and washed with brine (20 mL/mmol substrate) and water (20 mL/mmol substrate). The organic phases were combined, dried over anhydrous MgSO₄ and concentrated *in vacuo.*

**8-Ethyl 3a-isopropyl 2,2-diphenyl-1,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-3a,8(2H)-dicarboxylate (4)**

This compound was prepared according to general procedure G, using isopropyl 2-{(2-((ethoxycarbonyl)amino)phenyl)acrylate (60 mg, 0.22 mmol) as the Michael acceptor, (isocyanomethylene)dibenzene (42 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 72 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 4 as a yellow oil (63%, >20:1 d.r.).

**IR (neat) ν_{max} 1717, 1605, 1487, 1375, 1243, 1104, 905 cm⁻¹.**

**¹H NMR (400 MHz, CDCl₃) δ 7.45 (1H, d, J 7.5), 7.33-7.25 (2H, m), 7.24-7.16 (3H, m), 7.11 (1H, app. s), 7.06-6.96 (3H, m), 6.96-6.88 (3H, m), 6.81 (1H, t, J 7.4), 6.08 (1H, s), 4.85 (1H, sept, J 6.2), 4.36-4.19 (2H, m), 3.74 (1H, br s, NH), 3.14 (1H, d, J 13.0), 3.01 (1H, d, J 13.0), 1.39-1.27 (3H, m), 1.09 (6H, app. s).**
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.57 (1H, app. s), 7.34-7.22 (2H, m), 7.19-7.06 (4H, m), 7.00 (2H, d, $J$ 8.2), 6.92 (1H, t, $J$ 7.5), 6.84 (2H, d, $J$ 7.4), 6.22-6.07 (1H, s), 4.93 (1H, sept, $J$ 6.2), 4.56-4.18 (2H, m), 3.85 (1H, br s, NH), 3.26 (1H, d, $J$ 13.1), 3.00 (1H, d, $J$ 13.1), 2.31 (3H, s), 2.19 (3H, s), 1.34-1.27 (3H, m), 1.23-1.12 (6H, m).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 171.3, 152.5, 143.4, 141.7, 140.6, 139.8, 136.4, 135.8, 129.5, 129.3, 129.0, 128.8, 128.3, 123.5, 122.7, 114.7, 80.4, 70.0, 69.2, 62.0, 61.5, 49.8, 21.7, 20.9, 20.8, 14.7.

HRMS (ESI$^+$) 521.2421 ([M+Na]$^+$, C$_{31}$H$_{34}$N$_2$O$_4$Na requires 521.2416).

8-Ethyl 3a-isopropyl 2,2-di-p-tolyl-1,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-3a,8(2H)-dicarboxylate (5)

This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (60 mg, 0.22 mmol) as the Michael acceptor, 4,4’-(isocyanomethylene)bis(methylbenzene) (48 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 72 h. Column chromatography (petrol:ethyl acetate [6:1]) afforded the title compound 5 as a colourless oil (22%, >20:1 d.r.).

IR (neat) $\nu_{max}$ 2981, 1719, 1598, 1511, 1486, 1410, 1377, 1239, 1104, 1059, 908 cm$^{-1}$.

HRMS (ESI$^+$) 493.2098 ([M+Na]$^+$, C$_{29}$H$_{30}$N$_2$O$_4$Na requires 493.2103).
8-Ethyl 3a-isopropyl 2,2-bis(4-chlorophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-3a,8(2H)-dicarboxylate (6)

This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (60 mg, 0.22 mmol) as the Michael acceptor, 4,4’-(isocyanomethylene)bis(chlorobenzene) (57 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [6:1]) afforded the title compound 6 as a colourless oil (76%, >20:1 d.r.) in an inseparable mixture with a small amount of isopropyl 2,2-bis(4-chlorophenyl)-1-(p-tolylcarbamoyl)-1,2,3,4-tetrahydroquinoline-4-carboxylate.

IR (neat) \( \nu_{\text{max}} \) 1719, 1602, 1488, 1232, 1097, 904, 724 cm\(^{-1}\).

\( ^1\text{H} \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.42 (1H, app. s), 7.26-7.11 (6H, m), 7.05-6.95 (2H, m), 6.93-6.78 (3H, m), 6.12-5.99 (1H, m), 4.88 (1H, sept, \( J \) 6.2), 4.36-4.10 (2H, m), 3.80 (1H, br s, \( \text{N}H \)), 2.98 (2H, app. br s), 1.37-1.27 (3H, m), 1.13-1.07 (6H, m).

\( ^{13}\text{C} \) NMR (126 MHz, CDCl\(_3\)) \( \delta \) 171.1, 152.4, 144.8, 143.5, 141.3, 136.2, 132.9, 132.3, 129.7, 128.5, 127.7, 127.5, 127.3, 123.8, 123.0, 114.7, 81.0, 69.9, 69.5, 62.1, 61.6, 49.7, 21.6, 14.7.

HRMS (ESI\(^+\)) 561.1323 ([M+Na]\(^+\), \( C_{29}H_{28}Cl_2N_2O_4Na \) requires 561.1324).

8’-Ethyl 3a’-isopropyl 3’,3a’-dihydro-1’H-spiro[fluorene-9,2’-pyrrolo[2,3-b]indole]-3a’,8’(8a’H)-dicarboxylate (7)

This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (60 mg, 0.22 mmol) as the Michael acceptor, 9-isocyno-9H-fluorene (41 mg, 0.22
mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 7 as a yellow oil (54%, >20:1 d.r.).

IR (neat) ν_{max} 1716, 1582, 1487, 1330, 1250, 1103, 905 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 8.03 (1H, app. s), 7.66 (1H, d, J 7.5), 7.62-7.55 (2H, m), 7.43-7.35 (3H, m), 7.35-7.25 (2H, m), 7.17-7.07 (2H, m), 7.00 (1H, d, J 7.5), 6.62 (1H, s), 5.15 (1H, sept, J 6.3), 4.46-4.19 (2H, m), 3.22 (1H, d, J 13.9), 3.09 (1H, br s, NH), 2.78 (1H, d, J 13.9), 1.34-1.23 (9H, m).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) δ 171.9, 154.4, 152.8, 151.7, 149.5, 141.2, 139.2, 139.1, 129.6, 128.4, 128.3, 128.2, 128.0, 124.6, 124.2, 124.1, 123.2, 119.9, 119.5, 115.5, 82.2, 72.9, 69.7, 62.0, 61.7, 49.2, 21.6, 14.7.

HRMS (ESI\(^{+}\)) 491.1945 ([M+Na]\(^{+}\), \(\text{C}_{29}\text{H}_{28}\text{N}_{2}\text{O}_{4}\)Na requires 491.1947).

The reaction with 9-isocyanano-9H-fluorene and isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate formed 1'-'ethyl 4'-isopropyl 3',4'-dihydro-1'H-spiro[fluorene-9,2'-quinoline]-1',4'-dicarboxylate as a separable by-product in 34% yield.

IR (neat) ν_{max} 2982, 2129, 1729, 1590, 1520, 1452, 1220, 1104, 1062, 907 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 7.64-7.57 (3H, m), 7.56 (1H, app. s), 7.42-7.29 (4H, m), 7.20 (1H, t, J 7.6), 7.08 (1H, td, J 7.7, 1.4), 6.83 (1H, t, J 7.4), 6.70 (1H, app. s), 4.52 (1H, sept, J 6.2), 4.14 (2H, q, J 7.1), 3.49 (1H, dd, J 13.9, 8.3), 2.98-2.89 (1H, m), 2.67 (1H, dd, J 13.9, 3.4), 1.27 (3H, t, J 7.1), 0.87 (3H, d, J 6.2), 0.85 (3H, d, J 6.2).
$^1$H NMR (500 MHz, toluene-$d_8$, 363 K) δ 8.08-7.83 (2H, m), 7.35-7.23 (6H, m), 7.19-6.98 (8H, m), 6.93-6.79 (2H, m), 6.32 (1H, s), 6.26 (1H, s), 5.35-5.23 (2H, m), 5.12-5.01 (2H, m), 4.97-4.85 (2H, m), 3.64 (1H, br s, NH), 3.45 (3H, s), 3.36 (1H, d, J 13.3), 2.99 (3H, s), 2.90 (1H, d, J 12.9), 2.59 (1H, d, J 12.9), 2.13-2.09 (1H, m), 1.88-1.74 (2H, m), 1.03-0.95 (12H, m), 0.83 (6H, dd, J 16.1, 6.9), 0.74 (6H, dd, J 14.9, 6.9).

$^{13}$C NMR (126 MHz, toluene-$d_8$) δ 175.7, 174.7, 171.3, 171.1, 153.9, 152.1, 142.9, 141.8, 137.2, 137.0, 132.5, 132.0, 131.1, 129.5, 129.2, 128.5, 127.6, 125.4, 124.3, 123.9, 123.2, 123.1, 115.7, 114.8, 82.0,
HRMS (ESI\(^+\)) 503.2131 ([M+Na]\(^+\), \(\text{C}_{27}\text{H}_{32}\text{N}_{2}\text{O}_{6}\)Na requires 503.2153).

8-Ethyl 2-methyl 2-benzyl-3a-cyano-1,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-2,8(2H)-dicarboxylate (12)

This compound was prepared according to general procedure G, using ethyl (2-{1-cyanovinyl}phenyl)carbamate (39 mg, 0.18 mmol) as the Michael acceptor, methyl 2-isocynano-3-phenylpropanoate (34 mg, 0.18 mmol) as the isocyanide and 25% aqueous potassium hydroxide solution (0.5 mL) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [5:1]) afforded the title compound 12 as a colourless oil (72%, 1:1 d.r.).

IR (neat) \(\nu_{\text{max}}\) 2274, 2120, 1729, 1570, 1488, 1387, 1331, 1050, 840, 821, 754 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, toluene-\(d_8\), 363 K) \(\delta\) 7.98 (2H, app. s, Ar\(_{DS1,DS2}\)), 7.27 (2H, app. s, Ar\(_{DS1,DS2}\)), 7.14 (1H, app. s, Ar\(_{DS1}\)), 6.90 (2H, d, \(J\ 7.2\), Ar\(_{DS1}\)), 6.81 (1H, t, \(J\ 7.5\), Ar\(_{DS2}\)), 6.71 (1H, t, \(J\ 7.4\), Ar\(_{DS1}\)), \(^{\dagger}\), 5.91 (1H, s, \(\text{DS2}\)), 5.67 (1H, s, \(\text{DS1}\)), 4.20-3.94 (2H, m, \(\text{DS1}\)), 3.92-3.74 (2H, m, \(\text{DS2}\)), 3.49 (2H, br s, NH \(\text{DS1,DS2}\)), 3.42 (3H, s, \(\text{DS2}\)), 2.98-2.89 (2H, m), 2.85-2.71 (5H, m), 2.67 (1H, d, \(J\ 12.9\)), 2.43 (1H, d, \(J\ 12.9\)), 2.13 (1H, d, \(J\ 13.0\)), 1.90 (1H, d, \(J\ 13.1\)), 1.10-0.93 (6H, m, \(\text{DS1,DS2}\)).

\(^{\dagger}\)Remaining aromatic signals are buried under toluene peaks.

\(^{13}\)C NMR (126 MHz, toluene-\(d_8\), 363 K) \(\delta\) 174.3, 174.0, 151.5, 137.3, 137.2, 136.5, 136.1, 129.7, 129.7, 129.2, 128.5, 128.2, 127.4, 125.4, 124.1, 123.6, 123.5, 115.8, 114.9 [aromatics\(^{**}\)], 120.6, 120.4, 82.8, 82.2, 70.8, 69.8, 62.2, 61.5, 52.1, 51.5, 48.7, 48.6, 48.3, 47.5, 46.0, 44.6, 14.5, 14.4.

\(^{**}\)Remaining aromatic signals are buried under toluene peaks.
8-Ethyl 3a-isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-2,3a,8(2H)-tricarboxylate (13)

This compound was prepared according to general procedure G, using isopropyl 2-{2-((ethoxycarbonyl)amino)phenyl}acrylate (100 mg, 0.36 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (86 mg, 0.36 mmol) as the isocyanide and potassium carbonate (250 mg, 1.8 mmol) as the base. Reaction time was 24 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 13 as a yellow oil (57%, >20:1 d.r.).

IR ν\text{max} 2972, 2212, 1729, 1533, 1487, 1387, 1257, 1104, 1046, 840, 821 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (500 MHz, toluene-\textit{d}_8, 363 K) δ 7.85 (1H, app. s), 7.68 (1H, d, J 9.0), 7.31 (1H, d, J 7.2), 7.29-7.20 (1H, m), 7.16-7.07 (1H, m), 6.87 (1H, t, J 7.5), 6.45-6.38 (1H, m), 6.33 (1H, s), 4.87 (1H, sept, J 6.3), 4.22-4.04 (2H, m), 3.99 (1H, br s), 3.55 (1H, d, J 13.9), 3.13 (3H, s), 3.09 (1H, d, J 13.9), 1.12 (3H, t, J 7.1), 0.97 (3H, d, J 6.3), 0.91 (3H, d, J 6.3).

\textsuperscript{13}C NMR (126 MHz, toluene-\textit{d}_8, 363 K) δ 171.6, 170.2, 164.0 (d, J 254.3), 152.5, 145.0, 141.8, 140.9, 131.3 (d, J 9.3), 129.4, 127.0 (d, J 9.5), 123.5, 122.8, 115.5 (d, J 26.0), 114.6 (d, J 24.0), 114.6, 82.4, 71.1, 69.1, 61.3, 60.9, 51.7, 48.3, 20.5, 14.0.

\textsuperscript{19}F NMR (377 MHz, toluene-\textit{d}_8, \textit{\{\textsuperscript{1}H\})} δ -104.7.

HRMS (ESI\textsuperscript{+}) 538.1591 ([M+Na]\textsuperscript{+}, C\textsubscript{25}H\textsubscript{36}FN\textsubscript{8}O\textsubscript{8}Na requires 538.1602).
8-Ethyl 3a-isopropyl 2-methyl 2-(5-methyl-2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-
-b]indole-2,3a,8(2H)-tricarboxylate (14)

This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (50 mg, 0.18 mmol) as the Michael acceptor, methyl 2-isocyno-2-(5-methyl-2-nitrophenyl)acetate (42 mg, 0.18 mmol) as the isocyanide and potassium carbonate (120 mg, 0.87 mmol) as the base. Reaction time was 18 h. Column chromatography (petrol:ethyl acetate [7:2]) afforded the title compound 14 as a yellow oil (70%, >20:1 d.r.).

IR (neat) νmax 2982, 1722, 1523, 1486, 1346, 1239, 1103, 830, 754 cm⁻¹.

¹H NMR (500 MHz, toluene-d₈, 363 K) δ 7.88 (1H, app. s), 7.66 (1H, app. s), 7.35 (1H, d, J 7.5), 7.31-7.24 (1H, m), 7.14-7.11 (1H, m), 6.87 (1H, t, J 7.4), 6.64 (1H, d, J 8.2), 6.40 (1H, s), 4.87 (1H, sept, J 6.2), 4.24-4.03 (3H, m, OCH₂CH₃, NH), 3.61 (1H, d, J 13.7), 3.21-3.13 (4H, m), 1.98 (3H, s), 1.15 (3H, t, J 7.1), 0.99-0.89 (6H, m).

¹³C NMR (126 MHz, toluene-d₈, 363 K) δ 172.8, 170.3, 152.5, 147.3, 142.2, 142.0, 139.1, 136.5, 131.4, 129.4, 126.8, 123.6, 122.8, 122.5, 114.6, 82.2, 71.2, 68.9, 61.3, 60.9, 51.6, 48.4, 20.7, 20.5, 14.0.

HRMS (ESI⁺) 534.1855 ([M+Na]⁺, C₂₆H₂₉N₃O₈Na requires 534.1852).

8-Ethyl 3a-isopropyl 2-methyl 6-acetyl-2-(5-fluoro-2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-
-b]indole-2,3a,8(2H)-tricarboxylate (15)

This compound was prepared according to general procedure G, using isopropyl 2-(4-acetyl-2-(ethoxycarbonyl)amino)phenyl)acrylate (60 mg, 0.19 mmol) as
the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (44 mg, 0.19 mmol) as the isocyanide and potassium carbonate (130 mg, 0.94 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 15 as a yellow oil (61%, >20:1 d.r.).

IR (neat) $\nu_{max}$ 1731, 1668, 1539, 1437, 1255, 1094, 909 cm$^{-1}$.

$^1$H NMR (500 MHz, toluene-d$_8$, 363 K) $\delta$ 8.40 (1H, app. s), 7.70 (1H, d, $J$ 10.0), 7.53 (1H, d, $J$ 7.6), 7.34-7.27 (2H, m), 6.49-6.41 (1H, m), 6.34 (1H, s), 4.89 (1H, sept, $J$ 6.2), 4.21-4.04 (2H, m), 3.99 (1H, br s, NH), 3.55 (1H, d, $J$ 14.0), 3.13 (3H, s), 3.09 (1H, d, $J$ 14.0), 2.26 (3H, s), 1.14 (3H, t, $J$ 7.1), 1.00 (3H, d, $J$ 6.2), 0.94 (3H, d, $J$ 6.2).

$^{13}$C NMR (126 MHz, toluene-d$_8$, 363 K) $\delta$ 195.0, 171.4, 169.7, 164.1 (d, $J$ 254.1), 152.6, 144.9, 142.1, 140.8, 135.7, 131.1, 127.1 (d, $J$ 9.4), 123.4, 123.2, 115.4 (d, $J$ 26.2), 114.8 (d, $J$ 23.7), 114.3, 82.8, 71.0, 69.5, 61.7, 60.8, 51.7, 48.2, 25.5, 20.8, 20.7, 13.9.

$^{19}$F NMR (377 MHz, toluene-d$_8$, {1H}) $\delta$ -104.3.

HRMS (ESI$^+$) 558.1876 ([M+H]$^+$, $C_{27}$H$_{29}$FN$_3$O$_9$ requires 558.1888).

**8-Ethyl 3a-isopropyl 2-methyl 2-(2-nitrophenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-2,3a,8(2H)-tricarboxylate (16)**

This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (50 mg, 0.18 mmol) as the Michael acceptor, methyl 2-isocyano-2-(2-nitrophenyl)acetate (40 mg, 0.18 mmol) as the isocyanide and
potassium carbonate (120 mg, 0.87 mmol) as the base. Reaction time was 24 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 16 as a yellow oil (41%, 9:2 d.r. DS1:DS2).

IR (neat) \( \nu_{\text{max}} \): 1730, 1570, 1533, 1487, 1387, 1245, 1044, 840, 821, 753 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, toluene-\(d_8\), 363K) \( \delta \): 7.87 (1H, app. s, Ar\(_{\text{DS1}}\)), 7.69 (1H, d, J 8.0, Ar\(_{\text{DS2}}\)), 7.33 (1H, d, J 7.6, Ar\(_{\text{DS1}}\)), 7.27-7.19 (2H, m, Ar\(_{\text{DS1,DS2}}\)), 7.40 (1H, d, J 8.0, Ar\(_{\text{DS2}}\)), 7.33 (1H, d, J 7.6, Ar\(_{\text{DS1}}\)), 6.87 (1H, t, J 7.5, Ar\(_{\text{DS1}}\)), 6.84-6.75 (3H, m, Ar\(_{\text{DS1,DS2,DS2}}\)), 6.71 (1H, t, J 7.7, Ar\(_{\text{DS2}}\)), 6.45 (1H, s, DS2), 6.35 (1H, s, DS1), 4.99 (1H, sept, J 6.3, DS2), 4.87 (1H, sept, J 6.2, DS1), 4.25-4.02 (5H, m, DS1,DS2, NH\(_{\text{DS1}}\)), 3.97 (1H, d, J 13.7, DS2), 3.78 (1H, br s, NH\(_{\text{DS2}}\)), 3.55 (1H, d, J 13.7, DS1), 3.16-3.12 (4H, m, DS1,DS1), 2.53 (1H, d, J 13.7, DS2), 1.18-1.12 (6H, m, DS1,DS2), 0.98 (6H, J 6.3, DS1,DS2), 0.92 (6H, J 6.3, DS1,DS2). Remaining aromatic signals are buried under toluene peaks.

\(^{13}\)C NMR (126 MHz, toluene-\(d_8\), 363K) \( \delta \): 172.3, 172.1, 170.2, 170.2, 152.5, 149.4, 148.9, 142.0, 127.9, 124.2, 123.6, 123.2, 122.8, 122.5, 119.2, 114.6 [aromatics*], 82.1, 81.1, 71.1, 70.5, 69.0, 68.9, 61.1, 61.1, 60.9, 60.8, 51.7, 51.6, 48.4, 47.2 (C-8), 21.0, 20.9, 20.9, 20.8, 14.0, 14.0. *Remaining aromatic signals are buried under toluene peaks.

HRMS (ESI\(^+\)) 520.1687 ([M+Na]\(^+\), \( \text{C}_{25}\text{H}_{27}\text{N}_{3}\text{O}_{8}\text{Na} \) requires 520.1696).

8-Benzyl 3a-isopropyl 2-methyl 2-(2-methoxyphenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-2,3a,8(2H)-tricarboxylate (17)

This compound was prepared according to general procedure G, using isopropyl 2-((benzoxyl)carbonyl)amino)phenyl)acrylate (70 mg, 0.21 mmol) as the Michael acceptor, methyl 2-isocyano-2-(2-
methoxyphenyl)acetate (43 mg, 0.21 mmol) as the isocyanide and potassium carbonate (140 mg, 1.0 mmol) as the base. Reaction time was 24 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 17 as a colourless oil (49%, >20:1 d.r.).

IR (neat) ν_{max} 1728, 1602, 1480, 1352, 1247, 1105, 906 cm^{-1}.

^1{H} NMR (500 MHz, toluene-d_{8}, 363 K) δ 7.96 (1H, app. s), 7.59 (1H, d, J 7.6), 7.42 (1H, d, J 7.5), 7.32 (2H, d, J 7.4), 7.20-6.98 (5H, m), 6.87 (1H, t, J 7.5), 6.80 (1H, t, J 7.5), 6.59-6.47 (2H, m), 5.36-5.22 (1H, m), 5.20-5.07 (1H, m), 4.86 (1H, sept, J 6.2), 4.41 (1H, br s, NH), 3.61 (1H, d, J 13.1), 3.31 (3H, s), 3.04 (3H, s), 0.96 (3H, d, J 6.2), 0.90 (3H, d, J 6.2).

^13C NMR (126 MHz, toluene-d_{8}, 363 K) δ 173.6, 170.7, 157.2, 152.5, 144.2, 142.3, 136.7, 131.9, 128.7, 128.4, 128.2, 127.9, 127.7, 126.7, 123.7, 122.6, 120.8, 114.7, 111.7, 81.9, 69.8, 68.6, 67.0, 60.9, 54.9, 51.0, 46.8, 20.9.

HRMS (ESI^+) 567.2104 ([M+Na]^+, C_{31}H_{32}N_{2}O_{7}Na requires 567.2107).

8-Ethyl 3a-isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-6-(trifluoromethyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-2,3a,8(2H)-tricarboxylate (18)

This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)-4-(trifluoromethyl)phenyl)acrylate (60 mg, 0.17 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (41 mg, 0.17 mmol) as the isocyanide and potassium carbonate (120 mg, 0.87 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 18 as a yellow oil (48%, >20:1 d.r.).

IR (neat) ν_{max} 1730, 1532, 1450, 1324, 1258, 1169, 1130, 1065, 909 cm^{-1}.

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$^1$H NMR (500 MHz, toluene-d$_8$, 363 K) δ 8.16 (1H, app. s), 7.72-7.62 (1H, m), 7.32-7.23 (2H, m), 7.16 (1H, d, $J$ 7.9), 6.46-6.39 (1H, m), 6.31 (1H, s), 4.87 (1H, sept, $J$ 6.3), 4.15-3.99 (2H, m), 3.95 (1H, br s, NH), 3.51 (1H, d, $J$ 14.0), 3.11 (3H, s), 3.03 (1H, d, $J$ 14.0), 1.09 (3H, t, $J$ 7.1), 0.98 (3H, d, $J$ 6.3), 0.92 (3H, d, $J$ 6.3).

$^{13}$C NMR (126 MHz, toluene-d$_8$, 363 K) δ 171.4, 169.6, 164.1, 152.3, 144.8, 142.2, 140.7, 142.2, 140.7, 131.7 (q, $J$ 32.3), 131.3 (app. br s), 127.1 (d, $J$ 9.3), 124.1, 119.8 (q, $J$ 4.0), 115.3 (d, $J$ 26.7), 114.8 (d, $J$ 23.4), 111.4 (q, $J$ 3.9), 124.4 (q, $J$ 271.5, CF$_3$), 82.8, 71.0, 69.6, 61.9, 60.6, 51.7, 48.3, 20.8, 20.7, 13.8.

$^{19}$F NMR (377 MHz, toluene-d$_8$, $^{1}H$) δ -62.4, -102.5.

HRMS (ESI$^+$) 584.1670 ([M+H]$^+$, $C_{26}H_{26}F_4N_3O_8$ requires 584.1656).

3a-Isopropyl 2-methyl 8-benzoyl-2-(5-fluoro-2-nitrophenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2,3a-dicarboxylate (19)

This compound was prepared according to general procedure G, using isopropyl 2-(2-benzamidophenyl)acrylate (70 mg, 0.23 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (54 mg, 0.23 mmol) as the isocyanide and potassium carbonate (160 mg, 1.1 mmol) as the base. Reaction time was 16 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 19 as a yellow oil (57%, >20:1 d.r.).

IR (neat) $\nu_{max}$ 1728, 1635, 1587, 1528, 1480, 1350, 1244, 1135, 1100, 909 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.09-7.77 (2H, m), 7.59 (2H, app. d, $J$ 7.1), 7.55-7.38 (4H, m), 7.23 (1H, d, $J$ 7.1), 7.10-7.01 (1H, m), 7.00-6.82 (2H, m), 6.28 (1H, br s), 4.90 (1H, sept, $J$ 6.3), 3.86 (1H, br s, NH), 3.52 (1H, d, $J$ 14.4), 3.36 (3H, s), 2.90 (1H, d, $J$ 14.4), 1.13 (3H, d, $J$ 6.3), 1.02 (3H, d, $J$ 6.3).
\[ ^{13} \text{C NMR (101 MHz, CDCl}_3 \] \delta 171.6, 170.4, 169.6, 164.2 (d, J 253.5), 143.7, 142.6, 140.9, 136.0, 132.0, 131.1, 128.9, 128.7, 128.1, 127.6, 127.4, 124.1, 123.9, 116.0 (d, J 26.2), 115.4 (d, J 23.1), 84.1, 71.0, 69.8, 60.1, 53.0, 47.5, 21.5.

\[ ^{19} \text{F NMR (377 MHz, CDCl}_3 \] \delta -101.6.

HRMS (ESI\(^+\)) 570.1646 ([M+Na]\(^+\), \(C_{29}H_{26}FN_3O_7\)Na requires 570.1652).

8-Ethyl 3a-isopropyl 2-methyl 2-(2-(trifluoromethyl)phenyl)-1,3,3a,8a-tetrahydropyrrolo[2,3-b]indole-2,3a,8(2H)-tricarboxylate (20)

This compound was prepared according to general procedure G, using isopropyl 2-(2-((ethoxycarbonyl)amino)phenyl)acrylate (60 mg, 0.22 mmol) as the Michael acceptor, methyl 2-isocyno-2-(2-(trifluoromethyl)phenyl)acetate (53 mg, 0.22 mmol) as the isocyanide and potassium carbonate (150 mg, 1.1 mmol) as the base. Reaction time was 18 h. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 20 as a colourless oil (65%, >20:1 d.r.).

IR (neat) \( \nu_{\text{max}} \) 1731, 1564, 1487, 1311, 1244, 1105, 909 cm\(^{-1}\).

\[ ^{1} \text{H NMR (500 MHz, toluene-d}_8 \] \delta 8.00-7.78 (2H, m), 7.51 (1H, d, J 7.7), 7.36 (1H, d, J 7.5), 7.16-7.06 (2H, m), 6.95 (1H, t, J 7.4), 6.88 (1H, t, J 7.4), 6.45 (1H, s), 4.85 (1H, sept, J 6.2), 4.25-4.05 (3H, m, OCH_2CH_3, NH), 3.59 (1H, d, J 13.6), 3.14 (3H, s), 3.07 (1H, d, J 13.6), 1.14 (3H, t, J 6.2), 0.96 (3H, d, J 6.2), 0.88 (3H, d, J 6.2).

\[ ^{13} \text{C NMR (126 MHz, toluene-d}_8 \] \delta 172.8, 170.3, 152.6, 142.0, 141.5, 131.7, 131.4, 129.1, 128.8, 127.5, 127.3, 123.5, 122.7, 114.6 [aromatics*], 124.6 (q, J 273.3, CF\(_3\)), 82.1, 71.7, 68.8, 61.2, 60.9, 51.5, 48.5, 20.8, 20.7, 14.0. *Remaining aromatic signal is buried under toluene peaks.

\[ ^{19} \text{F NMR (377 MHz, CDCl}_3 \] \delta -55.6.
3a-Isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-8-(p-tolylcarbamoyl)-1,2,3,3a,8a-hexahydropyrrolo[2,3-b]indole-2,3a-dicarboxylate (21)

This compound was prepared according to general procedure G, using isopropyl 2-(2-(3-(p-tolyl)ureido)phenyl)acrylate (60 mg, 0.18 mmol) as the Michael acceptor, methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate (42 mg, 0.18 mmol) as the isocyanide and potassium carbonate (120 mg, 0.87 mmol) as the base. Reaction time was 2 h. Column chromatography (petrol:ethyl acetate [9:2]) afforded the title compound 21 as a colourless oil (54%, >20:1 d.r.).

IR (neat) ν_{max} 2280, 1618, 1539, 1329, 1243, 812 cm^{-1}.

{\textsuperscript{1}H} NMR (400 MHz, CDCl\textsubscript{3}) δ 7.75 (1H, dd, J 8.2, 5.1), 7.62 (1H, d, J 8.1), 7.49 (1H, dd, J 9.8, 2.7), 7.32 (2H, d, J 8.3), 7.28-7.20 (2H, m), 7.13-7.03 (4H, m), 6.96 (1H, t, J 7.5), 5.68 (1H, s), 4.88 (1H, sept, J 6.3), 3.50 (3H, s), 3.42 (1H, br s, NH), 3.37 (1H, d, J 14.2), 2.83 (1H, d, J 14.2), 2.25 (3H, s), 1.11 (6H, d, J 6.3).

{\textsuperscript{13}C} NMR (101 MHz) δ 171.2, 170.3, 164.0 (d, J 256.3), 152.2, 145.2, 141.6, 137.9, 135.3, 133.4, 130.8 (d, J 9.3), 129.8, 129.5, 127.6 (d, J 9.5), 124.3, 123.2, 120.3, 116.6 (d, J 25.9), 116.0 (d, J 23.4), 114.6, 82.1, 70.7, 70.2, 62.3, 53.4, 47.8, 21.5, 20.8.

{\textsuperscript{19}F} NMR (377 MHz, {\textsuperscript{1}H}) δ -103.4.

HRMS (ESI\textsuperscript{+}) 599.1910 ([M+Na]\textsuperscript{+}, C\textsubscript{36}H\textsubscript{28}FN\textsubscript{4}O\textsubscript{7}Na requires 599.1918).
4. Enantioselective reaction

**General Procedure H:** The relevant Michael acceptor substrate (1.0 eq), isocyanide (1.1 eq) and catalyst 29 (0.1 eq) were dissolved in toluene/CHCl₃/H₂O (14:5:1 v/v, 10 mL/mmol substrate) at -20 °C. After 10 minutes, K₂CO₃ (5.0 eq) was added, and the mixture was stirred at -20 °C until both substrates were consumed according to thin layer chromatography (24-48 h). The reaction mixture was then loaded directly onto a silica gel column and purified by flash chromatography.

**Catalyst synthesis:** Catalysts 24-31 were synthesized from the appropriate cinchona alkaloid according to the procedure by Chen and co-workers (S. Wu, D. Pan, C. Cao, Q. Wang, F.-X. Chen, *Adv. Synth. Catal. 2013, 355, 1917-1923*).

**Optimization reactions:** To a vial containing isopropyl 2-(2-(3-(p-tolyl)ureido)phenyl)acrylate (20 mg) in solvent (2 mL) was added methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanooacetate (1.1 eq.), the appropriate catalyst (10 mol %) and finally the base. The reaction was stirred at the appropriate temperature for 24 h before an aliquot was removed and purified by preparative TLC. The sample was analyzed by chiral stationary phase HPLC to determine the e.r. (see Section 6).
3a-Isopropyl 2-methyl 2-(5-fluoro-2-nitrophenyl)-8-(p-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2,3a-dicarboxylate (21)

This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(p-tolyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate as the isocyanide. Column chromatography (petrol:ethyl acetate [9:2]) afforded the title compound 21 as a colourless oil (60%, >20:1 d.r., 90:10 e.r.).

Data matched with those from the diastereoselective reaction.

2-Benzyl 3a-isopropyl 2-(5-fluoro-2-nitrophenyl)-8-(p-tolylcarbamoyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2,3a-dicarboxylate (32)

This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(p-tolyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and benzyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate as the isocyanide. The reaction was performed at 0 °C. Column chromatography (petrol:ethyl acetate [17:3]) afforded the title compound 32 as a colourless oil (54%, >20:1 d.r., 90:10 e.r.).

IR (neat) ν max 3401, 3270, 2981, 1733, 1593, 1530, 1479, 1345, 1238, 1103 cm⁻¹.

1H NMR (400 MHz, CDCl₃) δ 7.86 (1H, dd, J 8.9, 5.1), 7.63 (1H, d, J 7.7), 7.60 (1H, dd, J 9.0, 2.6), 7.41 (2H, d, J 8.4), 7.37-7.31 (2H, m), 7.31-7.29 (1H, m), 7.28-7.26 (1H, m), 7.23-7.11 (6H, m), 7.04 (1H, td, J 7.6, 0.8), 5.83 (1H, d, J 5.7), 5.06-4.98 (2H, m), 4.98 (1H, sept, J 6.3), 3.53 (1H, d, J 5.8), 3.44 (1H, d, J 14.3), 3.00 (1H, d, J 14.2), 2.36 (3H, s), 1.21 (3H, d, J 6.2), 1.19 (3H, d, J 6.1).
13C NMR (101 MHz, CDCl₃) δ 170.6, 170.3, 164.0 (d, J 254.8), 152.1, 145.1, 141.5, 138.2, 135.4, 134.7, 133.3, 129.8, 129.5, 128.5, 128.5, 127.6 (d, J 9.5), 124.3, 123.1, 120.1, 116.6 (d, J 26.0), 116.0 (d, J 23.3), 114.3, 82.3, 70.9, 70.2, 68.2, 62.2, 47.8, 21.5, 21.5, 20.9.

19F NMR (377 MHz, CDCl₃) δ -103.3 (ddd, J 9.8, 6.7, 4.9).

m/z HRMS (ESI⁺) 675.2222 ([M+Na]⁺, C₃₆H₃₃FN₄O₇Na requires 675.2225).

3a-Isopropyl 2-methyl 2-(2-nitrophenyl)-8-(p-tolylcarbamoyl)-1,2,3,3a,8a-hexahydropyrrolo[2,3-b]indole-2,3a-dicarboxylate (33)

This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(p-tolyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and methyl 2-isocyno-2-(2-nitrophenyl)acetate as the isocyanide. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 33 as a colourless oil (46%, 8.9:1 d.r., 93:7 e.r.).

Data are provided for major DS only.

IR (neat) νmax 3404, 3279, 1727, 1532, 1479, 1372, 1238, 1101 cm⁻¹.

1H NMR (400 MHz, CDCl₃) δ 7.84 (1H, d, J 8.1), 7.73 (1H, dd, J 7.9, 1.1), 7.68 (1H, dd, J 7.8, 1.3), 7.57 (1H, td, J 7.6, 1.3), 7.51-7.45 (3H, m), 7.43 (1H, br s), 7.36-7.28 (2H, m), 7.17 (2H, d, J 8.3), 7.03 (1H, td, J 7.5, 0.9), 5.58 (1H, s), 4.90 (1H, sept, J 6.2), 3.69 (1H, d, J 14.0), 3.63 (3H, s), 2.75 (1H, d, J 14.1), 2.34 (3H, s), 1.16 (3H, d, J 6.2), 1.12 (3H, d, J 6.3).

13C NMR (101 MHz, CDCl₃) δ 171.5, 170.3, 152.1, 149.7, 141.9, 135.5, 133.2, 131.8, 130.5, 129.9, 129.5, 129.5, 129.4, 129.2, 124.8, 124.2, 123.2, 120.3, 115.4, 81.7, 70.6, 70.0, 62.9, 53.4, 47.8, 21.5, 21.5, 20.9.
Diisopropyl 2-(5-fluoro-2-nitrophenyl)-8-(p-tolylcarbamoyl)-1,2,3,3a,8a-hexahydropyrrolo[2,3-b]indole-2,3a-dicarboxylate (34)

This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(p-tolyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and isopropyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate as the isocyanide. Column chromatography (petrol:ethyl acetate [17:3]) afforded the title compound 34 as a colourless oil (49%, >20:1 d.r., 92:8 e.r.).

On a 1.00 g scale (of isopropyl 2-(2-(3-(p-tolyl)ureido)phenyl)acrylate) this reaction afforded the title compound 34 in a 76 \% yield, >20:1 d.r., 92:8 e.r..

IR (neat) νmax 2280, 1618, 1539, 1329, 1243, 812 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.81 (1H, dd, J 8.8, 5.1), 7.72 (1H, d, J 8.1), 7.56 (1H, dd, J 9.8, 2.7), 7.42 (2H, d, J 8.4), 7.37-7.28 (3H, m), 7.22-7.11 (4H, m), 7.04 (1H, td, J 7.5, 0.8), 5.76 (1H, d, J 6.0), 4.97 (1H, sept, J 6.2), 4.90 (1H, sept, J 6.2), 3.43 (1H, d, J 6.1), 3.43 (1H, d, J 14.2), 2.92 (1H, d, J 14.2), 2.34 (3H, s), 1.21 (3H, d, J 6.3), 1.18 (3H, d, J 6.2), 1.10 (3H, d, J 6.3), 1.05 (3H, d, J 6.2).

¹³C NMR (101 MHz, CDCl₃) δ 170.4, 170.0, 163.9 (d, J 255.4), 152.1, 145.2 (d, J 4.4), 141.7, 135.4, 133.2, 130.7, 129.8, 129.5, 128.5 (d, J 9.2), 127.4 (d, J 9.3), 124.3, 124.3, 123.1, 120.2, 116.6 (d, J 25.8), 115.8 (d, J 23.1), 114.6, 82.3, 71.0, 70.7, 70.2, 62.4, 47.9, 21.5, 21.5, 21.3, 21.2, 20.8.

¹⁹F NMR (377 MHz, CDCl₃) δ -103.5 (m).

m/z HRMS (ESI⁺) 627.2228 ([M+Na]⁺, C₃₂H₃₃FN₄O₇Na requires 627.2225).
3a-Isopropyl 2-methyl 2-(4-chloro-2-nitrophenyl)-8-(p-tolylcarbamoyl)-1,2,3,3a,8a-hexahydropyrrolo[2,3-b]indole-2,3a-dicarboxylate (35)

This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(p-tolyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and methyl 2-(4-chloro-2-nitrophenyl)2-isocyanoacetate as the isocyanide. The reaction was performed at 0 °C. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 35 as a colourless oil (45%, >20:1 d.r., 86:14 e.r.).

IR (neat) $\nu_{\text{max}}$ 3401, 3269, 1728, 1531, 1485, 1364, 1240, 1105 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (1H, d, $J$ 7.9), 7.72 (1H, d, $J$ 8.5), 7.69 (1H, d, $J$ 2.2), 7.54 (1H, dd, $J$ 8.5, 2.2), 7.44 (2H, d, $J$ 8.4), 7.34-7.28 (3H, m), 7.17 (2H, d, $J$ 8.2), 7.04 (1H, td, $J$ 7.5, 0.8), 5.64 (1H, s), 4.93 (1H, sept, $J$ 6.2), 3.60 (3H, s), 3.57 (1H, d, $J$ 14.0), 2.81 (1H, d, $J$ 14.0), 2.34 (3H, s), 1.17 (3H, d, $J$ 6.2), 1.15 (3H, d, $J$ 6.2).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.2, 170.2, 152.0, 149.8, 141.8, 135.4, 135.2, 133.3, 131.9, 131.7, 130.5, 130.4, 129.9, 129.5, 124.9, 124.2, 123.2, 120.3, 115.1, 81.9, 70.4, 70.1, 62.7, 53.5, 47.7, 21.5, 21.5, 20.9.

$m/z$ HRMS (ESI$^+$) 615.1610 ([M+Na]$^+$, $C_{30}$H$_{29}$ClN$_4$O$_7$Na requires 615.1617).
3a-Isopropyl 2-methyl 2-(3-fluoro-2-nitrophenyl)-8-(p-tolylcarbamoyl)-1,2,3,3a,8a-hexahydropyrrolo[2,3-b]indole-2,3a-dicarboxylate (36)

This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(p-tolyl)ureido)phenyl)acrylate (50 mg mmol) as the Michael acceptor and methyl 2-(3-fluoro-2-nitrophenyl)-2-isocyanooacetate as the isocyanide. The reaction was performed at 0 °C. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 36 as a colourless oil (49%, 8.1:1 d.r., 67:37 e.r.).

Data are provided for major DS only.

IR (neat) νmax 3403, 3279, 2972, 1728, 1594, 1543, 1480, 1368, 1237, 1101 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.89 (1H, d, J 8.0), 7.52 (2H, d, J 8.5), 7.47 (1H, dd, J 8.2, 5.3), 7.43-7.37 (2H, m), 7.34-7.30 (1H, m), 7.30 (1H, td, J 7.8, 1.3), 7.27 (1H, td, J 8.3, 1.2), 7.18 (2H, d, J 8.3), 7.03 (1H, t, J 7.5), 5.62 (1H, s), 4.94 (1H, sept, J 6.2), 3.64 (1H, d, J 13.7), 3.60 (3H, s), 3.33 (1H, br s), 2.76 (1H, d, J 13.8), 2.34 (3H, s), 1.20 (3H, d, J 6.2), 1.14 (3H, d, J 6.2).

¹³C NMR (101 MHz, CDCl₃) δ 171.0, 170.2, 154.4 (d, J 258.6), 152.0, 142.1, 135.5, 133.2, 132.9, 131.2 (d, J 8.1), 130.0, 129.8, 129.5, 129.4, 124.4 (d, J 3.2), 124.2, 123.2, 120.5, 117.5 (d, J 19.5), 115.6, 81.5, 70.7, 70.1, 63.0, 53.6, 48.1, 21.5, 21.5, 20.9.

¹⁹F NMR (377 MHz, CDCl₃) δ -122.9 (m).

m/z HRMS (ESI⁺) 599.1926 ([M+Na]⁺, C₃₀H₂₉FN₄O₇Na requires 599.1912).
This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(p-tolyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and methyl 2-isocyano-2-(4-methyl-2-nitrophenyl)acetate as the isocyanide. Column chromatography (petrol:ethyl acetate [4:1]) afforded the title compound 37 as a colourless oil (83%, 10:1 d.r., 93:7 e.r.).

IR (neat) νmax, 3399, 3267, 1728, 1535, 1479, 1372, 1238, 1102 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.86 (1H, d, J 8.1), 7.56 (1H, d, J 8.1), 7.51-7.44 (4H, m), 7.38-7.27 (3H, m), 7.17 (2H, d, J 8.3), 7.02 (1H, td, J 7.5, 0.9), 5.55 (1H, s), 4.91 (1H, sept, J 6.2), 3.68 (1H, s), 3.63 (3H, s), 2.70 (1H, d, J 14.0), 2.42 (3H, s), 2.34 (3H, s), 1.18 (3H, d, J 6.2), 1.13 (3H, d, J 6.3).

¹³C NMR (101 MHz, CDCl₃) δ 171.7, 170.3, 152.1, 149.6, 141.9, 140.3, 135.6, 133.1, 132.3, 130.4, 129.8, 129.4, 129.0, 125.2, 124.2, 123.2, 120.3, 115.5, 81.7, 70.4, 69.9, 63.0, 53.4, 47.8, 21.5, 20.9, 20.8.

m/z HRMS (ESI⁺) 595.2174 ([M+Na]⁺, C₃₁H₃₂N₄O₇Na requires 595.2163).

This compound was prepared according to general procedure H, using isopropyl 2-(2-(3-(4-methoxyphenyl)ureido)phenyl)acrylate (50 mg) as the Michael acceptor and methyl 2-(5-fluoro-2-nitrophenyl)-2-isocyanoacetate as the isocyanide. Column chromatography
(petrol:ethyl acetate [4:1]) afforded the title compound 38 as a colourless oil (74%, >20:1 d.r., 90:10 e.r.).

IR (neat) $\nu_{\text{max}}$ 3402, 3282, 1727, 1677, 1514, 1479, 1372, 1232, 1101 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.82 (1H, dd, $J$ 8.8, 5.0), 7.73 (1H, d, $J$ 8.1), 7.56 (1H, dd, $J$ 9.8, 2.7), 7.45 (2H, d, $J$ 9.0), 7.34 (1H, d, $J$ 7.4), 7.32 (1H, ddd, $J$ 7.9, 7.7, 1.2), 7.20 (1H, s, NH), 7.16 (1H, ddd, $J$ 8.8, 6.9, 2.7), 7.04 (1H, td, $J$ 7.5, 0.8), 6.91 (2H, d, $J$ 9.0), 5.73 (1H, s), 4.96 (1H, sept, $J$ 6.2), 3.82 (3H, s), 3.60 (3H, s), 3.48 (1H, d, $J$ 14.2), 2.88 (1H, d, $J$ 14.2), 1.20 (3H, d, $J$ 6.3), 1.18 (3H, d, $J$ 6.2).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.1, 170.3, 163.9 (d, $J$ 254.9), 155.2, 152.3, 145.2 (d, $J$ 2.9), 141.7, 131.0, 130.7, 129.8, 128.5 (d, $J$ 9.8), 127.5 (d, $J$ 10.0), 124.3, 123.2, 122.1, 116.6 (d, $J$ 25.7), 116.0 (d, $J$ 23.4), 114.7, 114.2, 82.0, 70.6, 70.2, 62.4, 55.5, 53.4, 47.8, 21.5, 21.5.

$^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ -103.5 (m).

$m/z$ HRMS (ESI$^+$) 615.1855 ([M+Na]$^+$, $C_{30}H_{29}$FN$_4$NaO$_8$ requires 615.1862).
5. NMR Spectra of Novel Compounds
6. HPLC Traces

**Compound 21**

Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 25 % IPA in hexane, 1 mL/min

Retention times: 18.2 min, 23.9 min
Compound 32

Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 15% IPA in hexane, 1 mL/min

Retention times: 23.3 min, 32.8 min
Compound 33

Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 25 % IPA in hexane, 1 mL/min

Retention times: 30.1 min, 44.5 min
Compound 34

Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 15 % IPA in hexane, 1 mL/min

Retention times: 16.0 min, 24.0 min
Compound 35

Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 40 % IPA in hexane, 1 mL/min

Retention times: 19.7 min, 37.7 min
Compound 36

Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAC IC, 20 % IPA in hexane, 1 mL/min

Retention times: 16.1 min, 40.3 min
Compound 37

Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 40 % IPA in hexane, 1 mL/min

Retention times: 17.0 min, 29.8 min
Compound 38

Sample solution: 1 mg/mL in IPA/hexane 1:1

Column: CHIRALPAK IC, 15 % IPA in hexane, 1 mL/min

Retention times: 64.9 min, 71.8 min
7. Assignment of Stereochemistry

Assignment of relative stereochemistry of compounds was done by analogy to compounds 13 and 14, whose relative stereochemistry was unambiguously assigned by X-ray crystallography. The ring junction proton was used as a diagnostic shift in $^1$H NMR as follows:

As an illustration, comparison of several compounds is shown below. The major diastereomer exhibits a shift with a lower δ in $^1$H NMR.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$^1$H shift Major</th>
<th>$^1$H shift Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 (X-ray)</td>
<td>6.33</td>
<td>6.41</td>
</tr>
<tr>
<td>14 (X-ray)</td>
<td>6.40</td>
<td>6.50</td>
</tr>
<tr>
<td>16</td>
<td>6.35</td>
<td>6.45</td>
</tr>
<tr>
<td>33</td>
<td>5.58</td>
<td>6.12</td>
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<tr>
<td>36</td>
<td>5.62</td>
<td>6.13</td>
</tr>
<tr>
<td>37</td>
<td>5.55</td>
<td>6.11</td>
</tr>
<tr>
<td><strong>Lower δ</strong></td>
<td><strong>Higher δ</strong></td>
<td></td>
</tr>
</tbody>
</table>

Diagram:

![Diagram of compound structure with diagnostic proton in $^1$H NMR]
8. Thermodynamic Product

Information is provided for Scheme 1 in the main text. Pyrroloindoline 21 was synthesised according to Table 4 in 90:10 e.r.. The isolated product was then redissolved in toluene and TBAB (20 mol %), and K₂CO₃ (5.0 eq.) was added. The reaction was stirred for 48 h, after which all pyrroloindoline 21 had been consumed and a significant amount of an unidentified compound had been formed as a single diastereomer (>20:1 d.r.). This product was isolated and a single crystal was grown. Its identity was revealed by X-ray crystallographic analysis of this crystal as being that of pyrroline 39 (CCDC number 1020474). The e.r. of 39 was found to be 90:10 using chiral stationary phase HPLC.

During the development of the methodology, we noted that exchanging the Michael acceptor from a urea bearing a 4-MeC₆H₄- substituent to one featuring a 3,5-(CF₃)₂C₆H₃- group led to faster formation (24 h vs 48 h) of the thermodynamic spirocyclic pyrroline compound, but as a mixture of diastereomers (9:1 d.r.). Both diastereomers were crystallised and X-ray structures were obtained (CCDC numbers 1020475 and 1020476) to confirm that the formation of this thermodynamic product is a general phenomenon.
X-ray Crystallography

Crystals were mounted using the oil technique, in perfluoropolyether oil at 150(2) K (Cu and Mo) or 100(2) K (Synchrotron) with a Cryostream N₂ open-flow cooling device.

Molybdenum Radiation

Single crystal X-ray diffraction data were collected using graphite monochromated Mo-Ka radiation (0.71073 Å) using a Nonius KappaCCD diffractometer. Series of ω-scans were generally performed to provide sufficient data in each case to a maximum resolution of 0.77 Å. Data collection and cell refinement were carried out using DENZO-SMN. Intensity data were processed and corrected for absorption effects by the multi-scan method, based on multiple scans of identical and Laue equivalent reflections using SCALEPACK (within DENZO-SMN). Structure solution was carried out with direct methods using the programs SIR9219 within the CRYSTALS software suite. Refinement was carried out using full-matrix least-squares within the CRYSTALS suite on F2. In general, all non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were generally visible in the difference map and their positions and displacement parameters were refined using restraints prior to inclusion into the model using riding constraints.

Copper Radiation

Single crystal X-ray diffraction data were collected using graphite monochromated Cu K radiation (λ = 1.54184 Å) on an Oxford Diffraction SuperNova diffractometer. Series of ω-scans were performed in such a way as to collect all unique reflections to a maximum of 0.80 Å. Cell parameters and intensity data (including inter-frame scaling) were processed using CrysAlis Pro. The structures were solved by charge-flipping methods using SUPERFLIP and refined using full-matrix least-squares on F2 within the CRYSTALS suite. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were generally visible in the difference map and their positions and displacement parameters were refined using restraints prior to inclusion into the model using riding constraints.

Synchrotron Radiation

Single crystal X-ray diffraction data were collected using silicon double crystal monochromated synchrotron radiation (λ = 0.68890 Å) at Diamond Light Source beamline I19 using a custom-built Rigaku diffractometer equipped with a Cryostream N₂ open-flow cooling device. The data were collected via a series of ω-scans that were performed in such a way as to cover a full-sphere of data to a maximum resolution of 0.77 Å. Cell parameters and intensity data (including inter-frame scaling) were processed using CrysAlis Pro.8. The structures were solved by charge-flipping methods using SUPERFLIP and refined using full-matrix least-squares on F2 within the CRYSTALS suite. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were generally visible in the difference map and their positions and displacement parameters were refined using restraints prior to inclusion into the model using riding constraints.